Electronic supplementary information for the paper under the title:

Total Synthesis and Biological Evaluation of *atrop*-*O*-Benzyl-desmethylabyssomicin C

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1 General Experimental

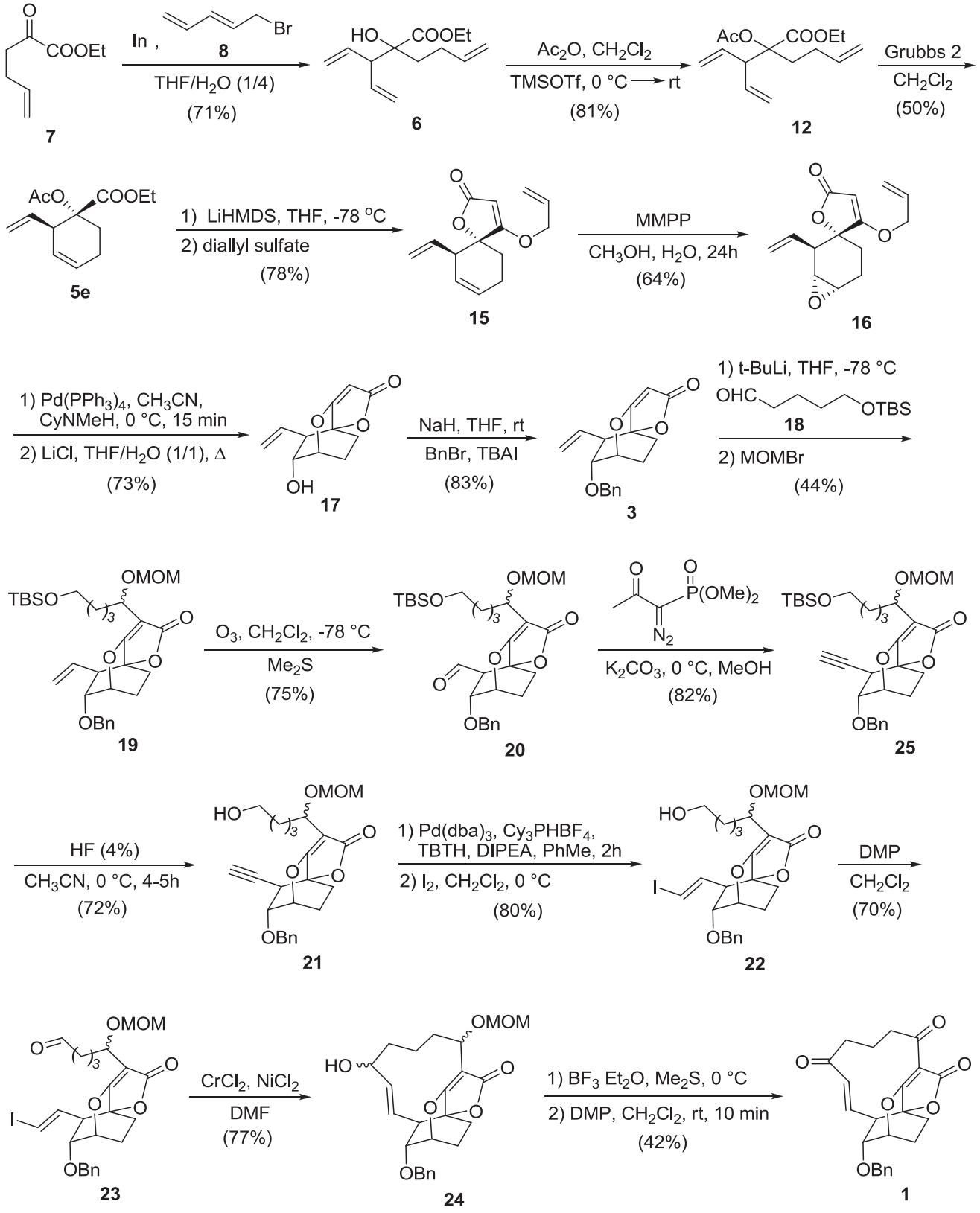
All chromatographic separations[1] were performed on Silica, 10-18, 60 Å (dry-flash) or 100–200, 60Å (column chromatography), ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents.[2] Petroleum ether refers to the fraction boiling at 70–72 °C. NMR spectra were recorded on a Varian Gemini 200 (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz) and on Bruker Avance III 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz), in deuterated chloroform. Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (*J*) are in Hz. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200). Microanalyses were performed at the Vario ELIII instrument CHNOS Elementar Analyzer, Elementar Analysensysteme GmbH, Hanau-Germany. Melting points were determined on a Kofler hot-stage and Electrothermal apparatus and are uncorrected.

X-ray crystal structure determination

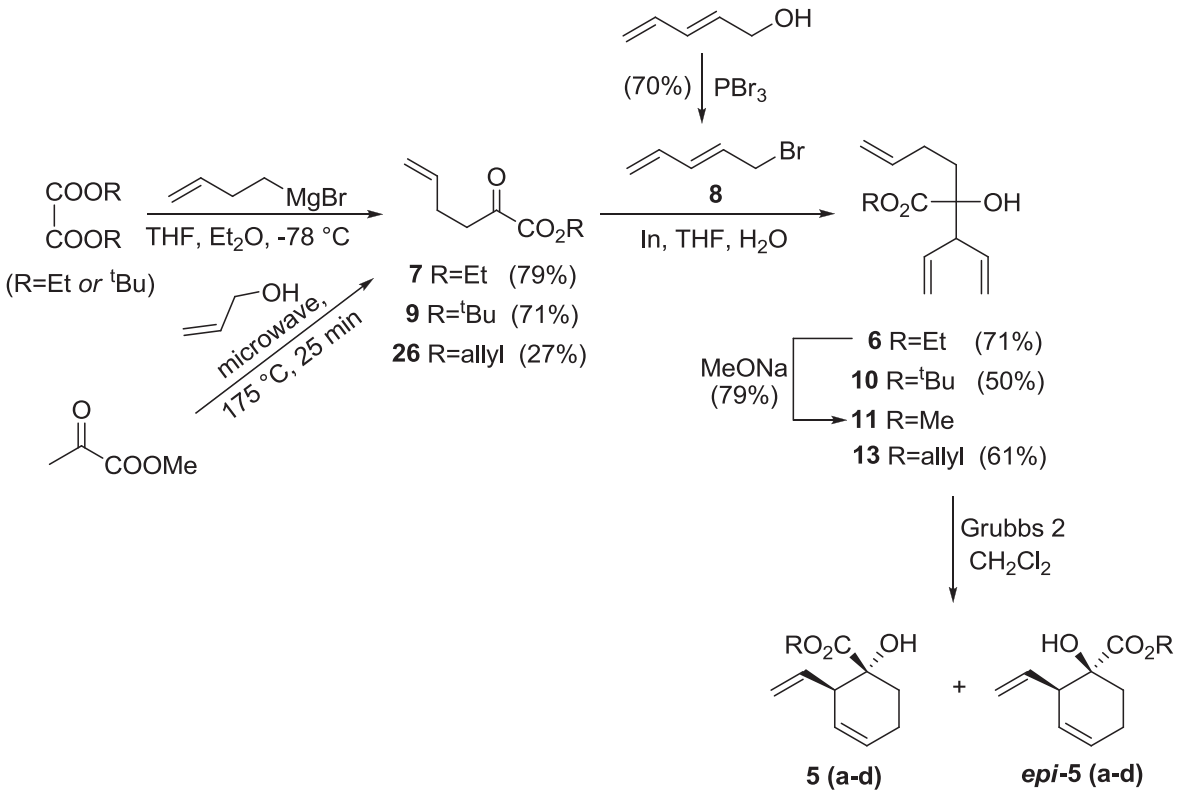
A single colorless crystal was selected and glued on glass fiber. Diffraction data were collected on an Oxford Diffraction KM4 four-circle goniometer equipped with Sapphire CCD detector. The crystal to detector distance was 45.0 mm and a graphite monochromated MoKα (λ = 0.71073 Å) X-radiation was employed in the measurements. The frame widths of 1° in ω, with 19 and 27 s were used to acquire each frame. More than a hemisphere of three-dimensional data was collected in all measurements. The data were reduced using the Oxford Diffraction program CrysAlisPro. A semiempirical absorption-correction based upon the intensities of equivalent reflections was applied, and the data were corrected for Lorentz, polarization, and background effects. Scattering curves for neutral atoms, together with anomalous-dispersion corrections, were taken from *International Tablesfor X-ray Crystallography*.[3] The structures were solved by direct methods,[4] and the figures were drawn using MERCURY.[5] Refinements were based on *F*2 values and done by full-matrix least-squares[6] with all non-H atoms anisotropic. The positions of all non H-atoms were located by direct methods. The positions of hydrogen atoms were found from the inspection of the difference Fourier maps. The final refinement included atomic positional and displacement parameters for all non-H atoms. The non-H atoms were refined anisotropically. However, at the final stage of the refinement, H atoms belonging to molecules were positioned geometrically (O−H = 0.82 and C−H = 0.93-0.97 Å) and refined using a riding model with fixed isotropic displacement parameters.

2 Experimental procedures

Scheme 1: Total synthesis of *atrop*-*O*-benzyl-desmethylabyssomicin C

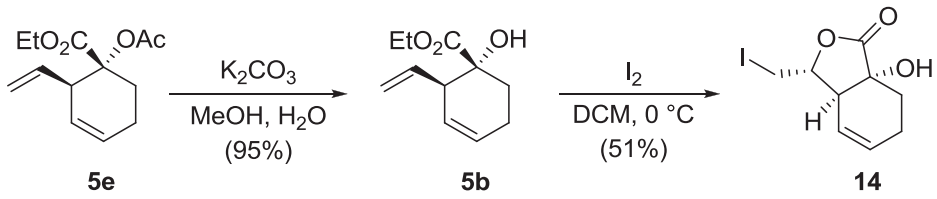


Scheme 2: Reactions not included in the main scheme

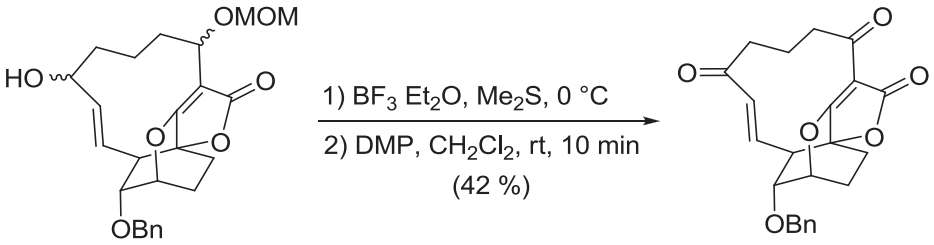


Substrate	Product	R	Yield	**5 : *epi*-5**
11	**5a/*epi*-5a**	Me	79%	1 : 2.7
6	**5b/*epi*-5b**	Et	84%	1 : 2.4*
10	**5c/*epi*-5c**	^{t}Bu	60%	1 : 2.4
13	**5d/*epi*-5d**	allyl	65%	1 : 2.8

*1 : 2.7 with Hoveyda-Grubbs 2 catalyst



2.1 11-(benzyloxy)-6,7,11,12,13,14-hexahydro-12,14a,3-(epoxymethyno)-2H-1-benzoxacyclododecyn-2,4,8(5H,10aH)-trione (1)



24 **1**

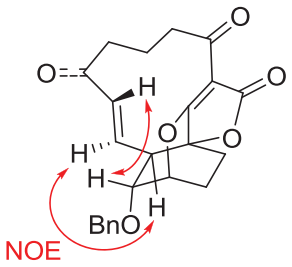
$BF_3 \cdot Et_2O$ (2.25 mg; 16 μmol; 2 eq) was added to a solution of MOM-protected alcohol **24** (3.5 mg; 8.0 μmol) in dimethylsulfide (0.5 mL) and the mixture was stirred at 0 °C for 4h. The solvent was removed on rotovap and the residue was dissolved in dichloromethane (0.5 mL). DMP (8.5 mg; 20 μmol; 2.5 eq) was added and the reaction mixture was stirred at room temperature for 10 min, diluted with ethyl acetate and washed with 10% $Na_2S_2O_3$ and water. The organic extract was dried over anhydrous $MgSO_4$, filtered, evaporated and the residue was purified by column chromatography (petroleum ether/ethyl acetate=1/1), yielding 1.3 mg (42%) of the diketone **1**, as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$): 7.39-7.33 (m, 4H), 7.26-7.23 (m, 1H), 6.40 (dd, J_1=16.5, J_2=6.5, 1H), 5.79 (d, J=17.0, 1H), 4.95-4.93 (m, 1H), 4.62 (d, J=12.0, 1H), 4.43 (d, J=12.0, 1H), 3.91-3.90 (m, 1H), 3.25-3.20 (m, 2H), 2.53-2.38 (m, 4H), 2.25-2.21 (m, 1H), 2.18-2.11 (m, 2H), 2.03-1.98 (m, 1H), 1.84-1.76 (m, 1H).

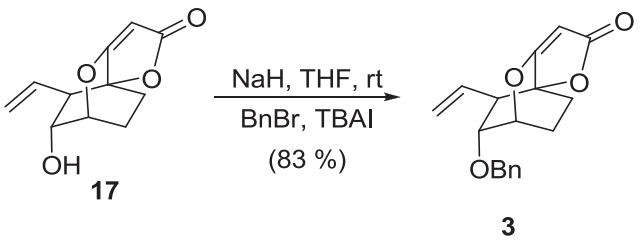
^{13}C NMR (125 MHz, $CDCl_3$): 201.2 (C), 194.6 (C), 183.5 (C), 168.8 (C), 136.1 (C), 135.7 (CH), 135.2 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 105.4 (C), 79.8 (C), 77.2 (CH), 75.5 (CH), 72.0 (CH_2), 48.5 (CH), 42.7 (CH_2), 38.5 (CH_2), 24.5 (CH_2), 20.5 (CH_2), 20.2 (CH_2).

HRMS (ESI): calcd. for $C_{23}H_{23}O_6$ $[M+H]^+$: 395.1489; found 395.1487.

IR$_{film}$: 2924, 2854, 1759, 1677, 1612, 1458, 1418, 1304, 1210, 1094, 1027, 988.



2.2 8-vinyl-6,7-dihydro-9-(benzyloxy)-5H-5,7a-ethano-2H-furo[3,2-b]pyran-2-one (3)



17 **3**

A mixture of sodium hydride (12 mg; 0.49 mmol; 1.5 eq) and alcohol **17** (68 mg; 0.33 mmol) in dry THF (0.6 mL) was stirred 30 min at room temperature, under argon. Benzyl bromide (84 mg; 0.49 mmol; 1.5 eq) and TBAI (12 mg; 0.033 mmol; 10 mol%) were added and stirring was continued for 1.5h. The reaction mixture was distributed between ethyl acetate and water, the aqueous layer was additionally extracted with ethyl acetate and the combined organic extract was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=4/1), to yield 80.9 mg (83%) of the benzyl ether **3**, as a white solid.

mp 70 °C.

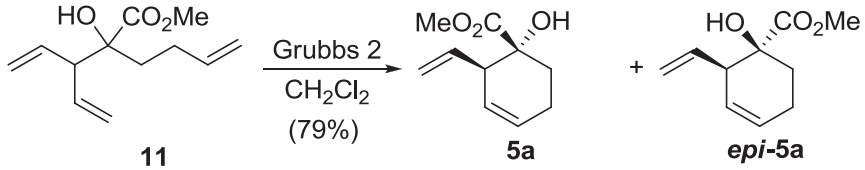
^{1}H NMR (500 MHz, $CDCl_3$): 7.37-7.28 (m, 5H), 5.49 (ddd, J_1=17.0, J_2=10.0, J_3=8.5, 1H), 5.26-5.21 (m, 2H), 4.98 (s, 1H), 4.65 (d, J=12.0, 1H), 4.59 (dt, J_1=3.5, J_2=1.5, 1H), 4.52 (d, J=11.5, 1H), 3.80 (dt, J_1=3.5, J_2=1.5, 1H), 2.85 (dd, J_1=8.5, J_2=3.5, 1H), 2.37-2.34 (m, 2H), 2.06-2.00 (m, 1H), 1.74-1.67 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): 180.8 (C), 172.8 (C), 137.0 (C), 132.8 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 120.0 (CH_2), 86.6 (CH), 78.3 (C), 77.9 (CH), 75.2 (CH), 71.5 (CH_2), 50.5 (CH), 28.2 (CH_2), 20.2 (CH_2).

HRMS (ESI): calcd. for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.1278; found 299.1287.

IR_{KBr}: 2946, 1763, 1651, 1588, 1459, 1400, 1210, 1177, 1068, 923.

2.3 Methyl 1-hydroxy-2-vinylcyclohex-3-enecarboxylate (5a, *epi*-5a)



11 **5a** ***epi*-5a**

A solution of methyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate **11** (42 mg; 0.2 mmol) in dry dichloromethane (1 mL) was stirred for 3.5 h in a presence of the 2nd generation Grubbs catalyst (0.85 mg; 1μmol; 5 mol%), under argon. The solvent was removed under reduced pressure and the residue

was purified by column chromatography (petroleum ether/ethyl acetate=95/5), to afford 29 mg (79%) of diastereomeric cyclohexanes **5a** and ***epi*-5a** (ratio determined by GC: 1/2.7).

Major diastereoisomer ***epi*-5a**

^{1}H NMR (500 MHz, $CDCl_3$): 5.87-5.73 (m, 2H), 5.50-5.46 (m, 1H), 5.18-5.07 (m, 2H), 3.78 (s, 3H), 3.30-3.25 (m, 1H), 2.98 (s, 1H, OH), 2.37-2.28 (m, 1H), 2.13-2.07 (m, 1H), 2.04-1.96 (m, 1H), 1,87-1.81 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): 176.3 (C), 136.2 (CH), 127.0 (CH), 126.1 (CH), 118.0 (CH_2), 74.3 (C), 52.8 (CH_3), 46.3 (CH), 30.8 (CH_2), 21.0 (CH_2).

HRMS (ESI): calcd. for $C_{10}H_{14}O_3Na$ $[M+Na]^+$: 205.0835; found 205.0832.

IR$_{film}$: 3518, 3026, 2953, 2928, 1733, 1636, 1439, 1258, 1210, 1101.

Minor diastereoisomer **5a**

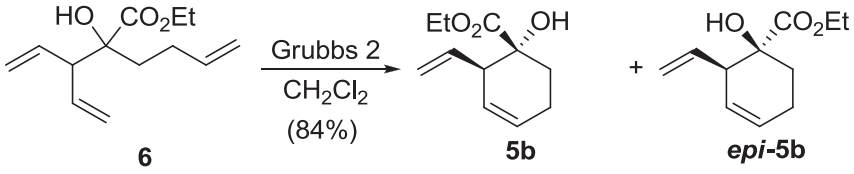
^{1}H NMR (500 MHz, $CDCl_3$): 5.85-5.80 (m, 1H), 5.64-5.50 (m, 2H), 5.11-5.05 (m, 2H), 3.72 (s, 3H), 3.04 (s, 1H, OH), 2.89-2.84 (m, 1H), 2.29-2.14 (m, 2H), 2.02-1.94 (m, 1H), 1.87-1.82 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): 175.0 (C), 136.3 (CH), 126.9 (CH), 125.4 (CH), 117.0 (CH_2), 75.1 (C), 51.6 (CH_3), 50.4 (CH), 27.0 (CH_2), 22.0 (CH_2).

HRMS (ESI): calcd. for $C_{10}H_{14}O_3$ $[M+H]^+$: 183.1015; found 183.1015.

IR$_{film}$: 3518, 3026, 2953, 2928, 1733, 1636, 1439, 1258, 1210, 1101.

2.4 Ethyl 1-hydroxy-2-vinylcyclohex-3-enecarboxylate (5b, *epi*-5b)



A solution of ethyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate **6** (50 mg; 0.23 mmol) in dry dichloromethane (1.2 mL) was stirred for 6 h in a presence of the second generation Grubbs catalyst (1 mg; 1.15 μmol; 5 mol%), under argon. The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate=9/1), to afford 37 mg (84%) of the diastereomeric cyclohexanes **5b** and ***epi*-5b** (ratio determined by GC: 1/2.4).

Major diastereoisomer ***epi*-5b**

^{1}H NMR (200 MHz, $CDCl_3$): 5.87-5.69 (m, 2H), 5.53-5.45 (m, 1H), 5.19-5.07 (m, 2H), 4.16 (m, 2H), 3.30-3.27 (m, 1H), 3.06 (s, 1H, OH), 2.45-2.23 (m, 1H), 2.18-1.94 (m, 2H), 1.89-1.78 (m, 1H), 1.30 (t, *J*=7.4, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): 176.3 (C), 136.3 (CH), 127.2 (CH), 126.3 (CH), 118.0 (CH_2), 74.1 (C), 61.9 (CH_2), 46.5 (CH), 31.0 (CH_2), 21.2 (CH_2), 14.2 (CH_3).

HRMS (ESI): calcd. for $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1172; found 197.1175.

IR$_{film}$: 3518, 3025, 2979, 2928, 1724, 1636, 1446, 1366, 1246, 1097, 1053, 919.

Elemental analysis: calcd for $C_{11}H_{16}O_3$: C 67.32%, H 8.22%; found: C 66.95%, H, 8.21%.

Minor diastereoisomer **5b**

^{1}H NMR (200 MHz, $CDCl_3$): 5.87-5.77 (m, 1H), 5.71-5.48 (m, 2H), 5.14-5.07 (m, 1H), 5.06-5.04 (m, 1H), 4.16 (dq, J_1=7.2, J_2=1.0, 2H), 3.22 (bs, 1H, OH), 2.92-2.82 (m, 1H), 2.26-2.16 (m, 2H), 2.05-1.78 (m, 2H), 1.27 (t, *J*=7.4, 3H).

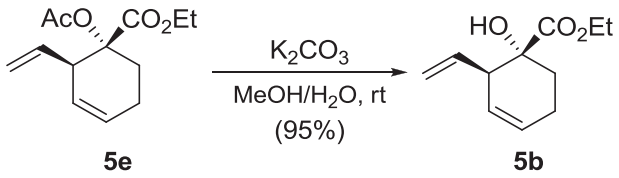
^{13}C NMR (50 MHz, $CDCl_3$): 174.9 (C), 136.7 (CH), 126.9 (CH), 125.7 (CH), 117.2 (CH_2), 74.9 (C), 61.3 (CH_2), 50.4 (CH), 26.9 (CH_2), 22.2 (CH_2), 14.0 (CH_3).

HRMS (ESI): calcd. for $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1172; found 197.1171.

IR$_{film}$: 3485, 3025, 2924, 2852, 1721, 1447, 1367, 1258, 1235, 1200, 1099, 1047, 921.

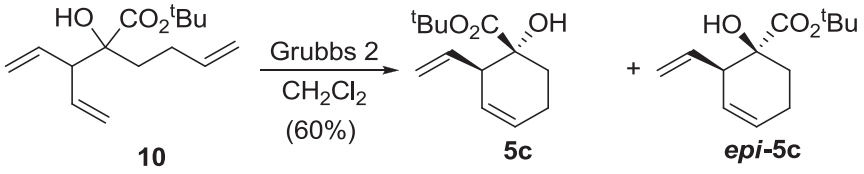
Elemental analysis: calcd for $C_{11}H_{16}O_3$: C 67.32%, H 8.22%; found: C 67.85%, H, 8.65%.

2.5 Ethyl 1-hydroxy-2-vinylcyclohex-3-enecarboxylate (5b) - hydrolysis of acetate 5e



A solution of potassium carbonate (12 mg; 0.084 mmol; 1 eq) in water (0.5 mL) was added to a solution of ethyl 1-acetoxy-2-vinylcyclohex-3-enecarboxylate **5e** (20 mg; 0.084 mmol) in methanol (1 mL) and the mixture was stirred for 10 minutes. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated on rotovap. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=4/1), to afford 15.6 mg (95%) of the alcohol **5b**, as a viscous oil.

2.6 *tert*-Butyl 1-hydroxy-2-vinylcyclohex-3-enecarboxylate (5c, *epi*-5c)



A solution of *tert*-butyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate **10** (67 mg; 0.265 mmol) in dry dichloromethane (2 mL) was stirred for 2.5 h in a presence of the second generation Grubbs catalyst (1.1 mg; 1.3 mmol; 5 mol%), under argon. The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate=95/5), to afford 36 mg (60%) of the diastereomeric cyclohexanes **5c** and ***epi*-5c** (ratio determined by GC: 1/2.4).

Major diastereoisomer ***epi*-5c**

^{1}H NMR (500 MHz, $CDCl_3$): 5.86-5.64 (m, 2H), 5.54-5.46 (m, 1H), 5.17-5.05 (m, 2H), 3.25-3.21(m, 1H), 3.16 (s, 1H, OH), 2.38-2.04 (m, 2H), 2.00-1.89 (m, 1H), 1.87-1.76 (m, 1H), 1.47 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): 175.6 (C), 136.5 (CH), 127.1 (CH), 126.6 (CH), 117.7 (CH_2), 82.4 (C), 73.9 (C), 46.7 (CH), 31.2 (CH_2), 28.0 (CH_3), 21.4 (CH_2).

Minor diastereoisomer **5c**

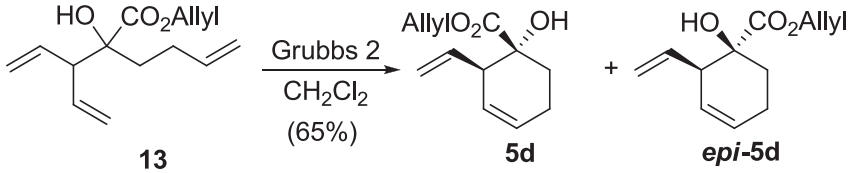
^{1}H NMR (500 MHz, $CDCl_3$): 5.86-5.64 (m, 2H), 5.54-5.46 (m, 1H), 5.17-5.05 (m, 2H), 3.26 (s, 1H, OH), 2.89-2.84 (CH, 1H), 2.38-2.04 (m, 2H), 2.00-1.89 (m, 1H), 1.87-1.76 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): 1743.6 (C), 136.9 (CH), 126.8 (CH), 126.2 (CH), 117.0 (CH_2), 82.6 (C), 74.6 (C), 50.4 (CH), 31.2 (CH_2), 28.1 (CH_3), 22.9 (CH_2).

HRMS (ESI): calcd. for $C_{13}H_{20}O_3Na$ $[M+Na]^+$: 247.1304; found 247.1306.

IR$_{film}$: 3509, 3025, 2977, 2930, 1719, 1653,1634, 1370, 1278, 1255, 1164, 1101.

2.7 Allyl 1-hydroxy-2-vinylcyclohex-3-enecarboxylate (5d, *epi*-5d)



A solution of allyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate **13** (30 mg; 0.127 mmol) in dry dichloromethane (1.0 mL) was stirred for 2.5 h in a presence of the second generation Grubbs catalyst (0.5 mg, 0.64 μmol; 5 mol%), under argon. The solvent was removed under reduced pressure and the

residue was purified by column chromatography (petroleum ether/ethyl acetate=95/5), to afford 17.5 mg (65%) of the diastereomeric cyclohexanes **5d** and ***epi*-5d** (ratio determined by GC: 1/2.8).

Major diastereoisomer ***epi*-5d**

^{1}H NMR (200 MHz, $CDCl_3$): 6.03-5.70 (m, 3H), 5.55-5.07 (m, 5H), 4.69 (d, *J*=5.1, 2H), 3.37-3.24 (m, 1H), 3.02 (s, 1H, OH), 2.45-2.24 (m,1H), 2.21-2.10 (m, 1H), 2.10-1.94 (m, 1H),1.93-1.80 (m, 1H).

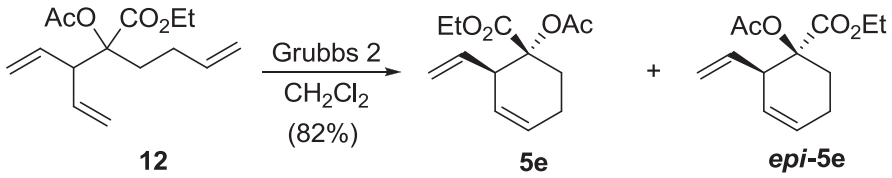
IR_{film}: 3502, 3056, 2980, 1726, 1641, 1223, 1034, 915.

Minor diastereoisomer **5d**

^{1}H NMR (200 MHz, $CDCl_3$): 6.03-5.78 (m, 2H), 5.72-5.47 (m, 2H), 5.40-5.03 (m, 4H), 4.73-4.53 (m, 2H), 3.07 (s, 1H, OH), 2.95-2.83 (m,1H), 2.30-2.16 (m, 2H), 2.04-1.80 (m, 2H).

IR_{film}: 3501, 3058, 2980, 1726, 1640, 1223, 1034, 915.

2.8 Ethyl-1-acetoxy-2-vinylcyclohexanecarboxylate (5e, *epi*-5e)



The 2nd generation Grubbs catalyst (16 mg; 0.0188 mmol ; 0.5% mol) was added to a solution of ethyl 2-acetoxy-2-(penta-1,4-dien-3yl)hex-5-enoate **12** (1.0 g; 3.76 mmol) in dry dichloromethane (10 mL) and the mixture was stirred under argon for 5h. The solvent was removed on rotovap and the residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=9/1), to yield 0.74 g (82%) of the diastereoisomeric mixture (ratio of **5e**/***epi*-5e** determined by GC: 1.8/1). After medium pressure liquid chromatography, 0.45 g (50%) of **5e** and 0.25 g (28%) of ***epi*-5e** were isolated.

Major diastereoisomer **5e**

^{1}H NMR (200 MHz, $CDCl_3$): 5.84-5.77 (m, 1H), 5.63-5.45 (m, 2H), 5.16-5.08 (m, 2H), 4.16 (q, *J*=7.2, 2H), 3.02 (bt, *J*=5.6, 1H), 2.52-2.40 (m, 1H), 2.19-1.91 (m, 3H), 2.08 (s, 3H), 1.25 (t, *J*=7.4, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): 170.7 (C), 169.9 (C), 134.9 (CH), 126.6 (CH), 125.1 (CH), 118.7 (CH_2), 80.8 (C), 60.7 (CH_2), 47.3 (CH), 21.9 (CH_2), 21.5 (CH_2), 20.7 (CH_3), 13.9 (CH_3).

HRMS (ESI): calcd. for $C_{13}H_{18}O_4Na$ $[M+Na]^+$: 261.1097; found 261.1100.

IR_{film}: 3028, 2981, 2843, 1743, 1636, 1370, 1267, 1242, 1189, 1063, 926.

Elemental analysis: calcd for $C_{13}H_{18}O_4$: C 65.53%, H 7.61%; found: C 65.06%, H, 7.21%.

Minor diastereoisomer ***epi*-5e**

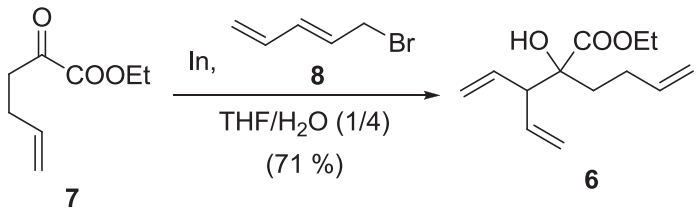
^{1}H NMR (200 MHz, $CDCl_3$): 5.85-5.67 (m, 2H), 5.52-5.44 (m, 1H), 5.12 (bs, 1H), 5.08-5.03 (m, 1H), 4.19 (q, *J*=7.4, 2H), 3.52-3.48 (m, 1H), 2.35-2.24 (m, 1H), 2.09-1.93 (m, 3H), 2.04 (s, 3H), 1.25 (t, *J*=7.4, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): 170.7 (C), 169.7 (C), 135.9 (CH), 127.1 (CH), 125.6 (CH), 117.2 (CH_2), 80.5 (C), 61.0 (CH_2), 45.8 (CH), 26.8 (CH_2), 22.1 (CH_2), 20.7 (CH_3), 13.9 (CH_3).

HRMS (ESI): calcd. for $C_{13}H_{18}O_4Na$ $[M+Na]^+$: 261.1097; found 261.1086.

IR$_{film}$: 3196, 2923, 2852, 1743, 1659, 1633, 1465, 1266, 1241, 1188, 1064, 923.

2.9 Ethyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate (6)



A mixture of ethyl 2-oxohex-5-enoate **7** (0.77 g; 4.92 mmol), *(E)*-5-bromopenta-1,3-diene **8** (1.0 g; 6.87 mmol; 1.4 eq) and indium (0.678 g; 5.9 mmol; 1.2 eq) in THF/H_2O mixture (15 mL; 1/4) was stirred vigorously for 4 h. The reaction mixture was diluted with ethyl acetate, washed with saturated NH_4Cl and the aqueous layer was additionally extracted with ethyl acetate (3x20 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate = 95/5) to afford alcohol **6** (0.677 g, 71%), as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): 5.98-5.67 (m, 3H), 5.20-4.91 (m, 6H), 4.22 (q, *J*=7.2, 2H), 3.32 (s, 1H, OH), 3.00 (t, *J*=8.6, 1H), 2.28-2.09 (m, 1H), 1.84-1.68 (m, 3H), 1.30 (t, *J*=7.4, 3H).

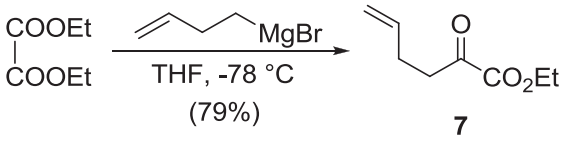
^{13}C NMR (50 MHz, $CDCl_3$): 175.7 (C), 137.9 (CH), 136.0 (CH), 135.4 (CH), 117.9 (CH_2), 117.1 (CH_2), 114.8 (CH_2), 78.8 (C), 61.9 (CH_2), 57.0 (CH), 36.3 (CH_2), 27.9 (CH_2), 14.2 (CH_3).

HRMS (ESI): calcd. for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1485; found 225.1482.

IR$_{film}$: 3513, 3077, 2979, 2931, 1725, 1639, 1241, 1206, 1093, 998, 913.

Elemental analysis: calcd for $C_{13}H_{20}O_3$: C 69.61%, H 8.99%; found: C 69.29%, H, 8.91%.

2.10 Ethyl 2-oxohex-5-enoate[7] (7)



7

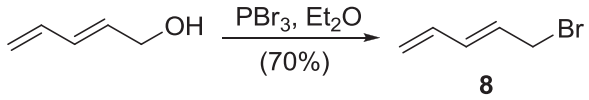
A solution of but-3-enylmagnesium bromide (obtained from homoallyl bromide (12 g; 89 mmol; 1.2 eq) and magnesium (4.8 g; 200 mmol; 2.7 eq) in dry THF (80 mL)) was added to a cold (-78 °C) solution of diethyl oxalate (10.7 g; 73.6 mmol) in THF (50 mL) and ether (100 mL). The reaction mixture was stirred at -78 °C for 4h and quenched with saturated NH_4Cl (50 mL). The aqueous layer was extracted with ether and the combined organic extract was dried over anhydrous $MgSO_4$. After distillation under reduced pressure (bp 114 °C/40 mmHg), the pure product **7** (9.1 g; 79%) was obtained, as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): 5.85 (m, 1H), 5.1(m, 2H), 4.3 (q, *J*=7.4, 2H), 2.9 (t, *J*=7.4, 2H), 2.4 (t, *J*=7.4,2H), 1.4 (t, *J*=7.4, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): 193.8 (C), 160.9 (C), 136.0 (CH), 115.8 (CH_2), 62.3 (CH_2), 38.3 (CH_2), 26.8 (CH_2), 13.8 (CH_3).

IR_{film}: 1741, 1730, 1682.

2.11 (*E*)-5-bromopenta-1,3-diene[8] (8)



8

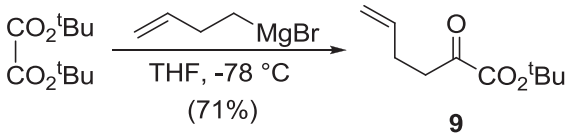
Phosphorus tribromide (3.3 mL; 0.035 mol; 0.61 eq) was added dropwise to an ice-cold solution of (*E*)-penta-2,4-dien-1-ol[9] (4.8 g; 0.057 mol) in dry ether (60 mL) and the mixture was stirred for 1h. Water (20 mL) was added and the product was extracted with ether (3x15 mL). The organic extract was washed with water and brine, dried over anhydrous $MgSO_4$ and the product (5.9 g, 70%) was isolated as a colorless liquid by distillation under reduced pressure (bp 56-57 °C/38 mmHg).

^{1}H NMR (200 MHz, $CDCl_3$): 6.37-6.24 (m, 2H), 5.95-5.84 (m, 1H), 5.31-5.25 (m, 1H), 5.18-5.15 (m, 1H), 4.03 (d, *J*=7.5, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): 135.4 (CH), 135.1 (CH), 129.0 (CH), 119.3 (CH_2), 32.7 (CH_2).

IR_{film}: 3013, 2968, 1601,1255, 1203, 1002, 970.

2.12 *tert*-Butyl 2-oxohex-5-enoate[10] (9)



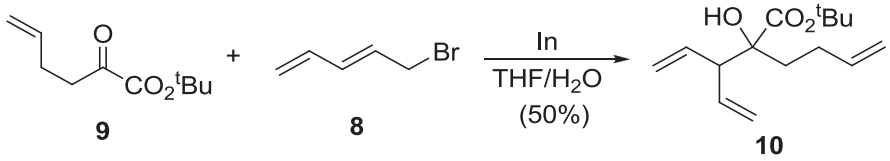
A solution of but-3-enylmagnesium bromide (obtained from homoallyl bromide (2.43 g; 18 mmol; 1.2 eq) and magnesium (1.0 g; 40 mmol; 2.7 eq) in dry THF (15 mL)) was added to a cold (-78 °C) solution of di-*tert*-butyl oxalate (3.0 g; 15 mmol) in THF (15 mL) and ether (25 mL), under argon. After 4 h of stirring, the reaction was quenched with saturated NH_4Cl (25 mL) and the aqueous layer was extracted with ether. The organic extract was dried over $MgSO_4$, filtered, concentrated on rotovap, and the residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=95/5), to afford 1.95 g (71%) of the pure product, as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): 5.90-5.72 (m, 1H), 5.11-4.96 (m, 2H), 2.89 (t, *J*=7.3, 2H), 2.44-2.31 (m, 2H), 1.55 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): 160.5 (C), 136.0 (CH), 115.5 (CH_2), 83.6 (C), 38.3 (CH_2), 27.7 (CH_3), 27.0 (CH_2). The signal corresponding to C-2 atom could not be detected under the recording conditions.

IR$_{film}$: 3080 2982, 1721, 1642, 1137, 1070.

2.13 *tert*-butyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate (10)



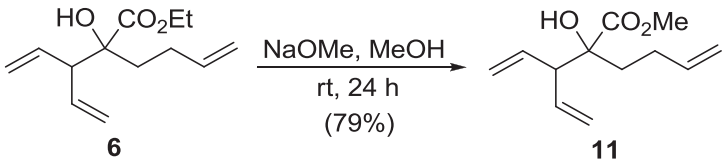
A suspension of *tert*-butyl 2-oxohex-5-enoate **9** (100 mg; 0.54 mmol), (*E*)-5-bromopenta-1,3-diene **8** (119 mg; 0.81 mmol; 1.5 eq) and indium (68 mg; 0.7 mmol; 1.3 eq) in THF/H_2O mixture (2.5 mL; 1/4) was stirred vigorously for 4-5h. The reaction mixture was diluted with ethyl acetate and washed with saturated ammonium chloride. The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=95/5), to give 69 mg (50%) of the alcohol **10**, as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): 6.01-5.69 (m, 3H), 5.19-4.90 (m, 6H), 3.38 (s, 1H, OH), 3.04-2.88 (m, 1H), 2.34-2.11 (m, 1H), 1.88-1.54 (m, 3H), 1.48 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): 174.7 (C), 138.1 (CH), 136.0 (CH), 135.7 (CH), 117.3 (CH_2), 116.8 (CH_2), 114.6 (CH_2), 82 (C), 78.0 (C), 56.9 (CH), 36.5 (CH_2), 27.9 (CH_3), 27.7 (CH_2).

IR$_{film}$: 3505, 3077, 2979, 2931, 1721, 1640, 1371, 1255, 1155, 916.

2.14 Methyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate (11)



A solution of ethyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate **6** (56 mg; 0.25 mmol) and sodium methoxide (135 mg; 2.5 mmol; 10 eq) in dry methanol (2 mL) was stirred 24h at rt. The reaction mixture was evaporated to dryness and the residue was distributed between dichloromethane and water. The organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=1/1), to yield 42 mg (79%) of the methyl ester **11**, as a colorless oil.

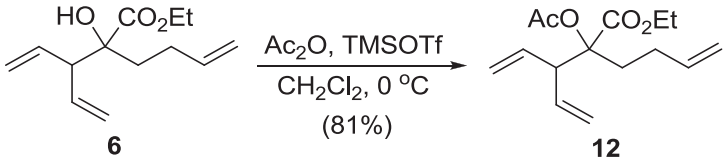
^{1}H NMR (200 MHz, $CDCl_3$): 6.02-5.64 (m, 3H), 5.25-4.87 (m, 6H), 3.76 (s, 3H), 3.28 (bs, 1H, OH), 3.08- 2.92 (m, 1H), 2.32-2.09 (m, 1H), 1.91-1.67 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): 175.9 (C), 137.6 (CH), 135.8 (CH), 135.0 (CH), 118.1 (CH_2), 117.1 (CH_2), 114.8 (CH_2), 79.3 (C), 57.0 (CH_3), 52.4 (CH), 36.2 (CH_2), 27.8 (CH_2).

HRMS (ESI): calcd. for $C_{12}H_{18}O_3Na$ $[M+Na]^+$: 233.1148; found 233.1148.

IR_{film}: 3503, 3027, 2948, 1731, 1638, 1210, 1155, 998.

2.15 Ethyl 2-acetoxy-2-(penta-1,4-dien-3-yl)hex-5-enoate (12)



Trimethylsilyl triflate (0.326 g; 1.46 mmol; 0.3 eq) was added to a solution of alcohol **6** (1.1 g; 4.91 mmol) and acetic anhydride (2.0 g; 19.6 mmol; 4 eq) in dry dichloromethane (10 mL), while cooling in an ice bath. The reaction mixture was stirred 10 min at 0 °C, and then 10 min at room temperature. The reaction mixture was distributed between dichloromethane and water and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed on rotovap and the residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=9/1), to yield 1.06 g (81%) of the pure acetate **12**, as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): 5.99 (ddd, J_1=16.8, J_2=10.0, J_3=6.6, 1H), 5.89-5.66 (m, 2H), 5.21-4.93 (m, 6H), 4.18 (q, J=7.4, 2H), 3.43 (t, J=7.2, 1H), 2.40-1.94 (m, 4H), 2.08 (s, 3H), 1.25 (t, J=7.2, 3H).

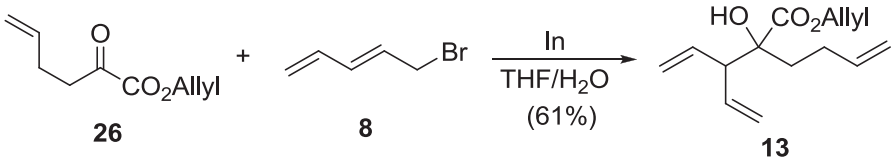
^{13}C NMR (50 MHz, $CDCl_3$): 170.1 (C), 169.6 (C), 137.6 (CH), 135.1 (CH), 134.4 (CH), 118.3 (CH_2), 117.4 (CH_2), 114.9 (CH_2), 83.7 (C), 61.1 (CH_2), 52.8 (CH), 31.4 (CH_2), 27.4 (CH_2), 21.0 (CH_3), 14.0 (CH_3).

HRMS (ESI): calcd. for $C_{15}H_{23}O_4$ $[M+H]^+$: 267.1591; found 267.1596.

IR$_{film}$: 3080, 2981, 1742, 1640, 1369, 1250, 1215, 1027, 998, 919.

Elemental analysis: calcd for $C_{15}H_{22}O_4$: C 67.64%, H 8.33%; found: C 67.25%, H, 8.71%.

2.16 Allyl 2-hydroxy-2-(penta-1,4-dien-3-yl)hex-5-enoate (13)



26 **8** **13**

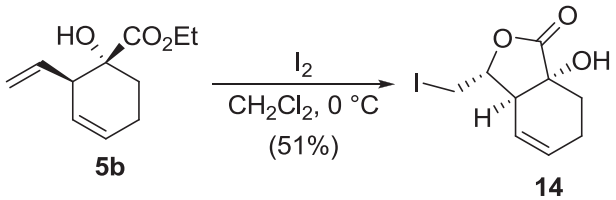
A suspension of allyl 2-oxohex-5-enoate **26** (35 mg; 0.21 mmol), *(E)*-5-bromopenta-1,3-diene **8** (45 mg; 0.31 mmol; 1.5 eq) and indium (26.2 mg; 0.23 mmol; 1.1 eq) in THF/H_2O mixture (2.5 mL; 1/4) was stirred vigorously for 4-5h. The reaction mixture was diluted with ethyl acetate and washed with saturated ammonium chloride. The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=9/1), to give 29 mg (61%) of the alcohol **13**, as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): 6.04-5.66 (m, 4H), 5.43-4.90 (m, 8H), 4.70-4.61 (m, 2H), 3.28 (s, 1H, OH), 3.02 (t, *J*=8.8, 1H), 2.30-2.10 (m, 1H), 1.87-1.68 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): 175.1 (C), 137.8 (CH), 135.8 (CH), 135.0 (CH), 131.5 (CH), 119.3 (CH_2), 118.1 (CH_2), 117.1 (CH_2), 114.9 (CH_2), 79.0 (C), 66.5 (CH_2), 57.2 (CH), 36.3 (CH_2), 27.9 (CH_2).

IR$_{film}$: 3512, 2975, 1733, 1617, 1265, 849, 737.

2.17 7a-hydroxy-3-(iodomethyl)-3,3a,7,7a-tetrahydroisobenzofuran-1(6H)-one (14)



5b **14**

A solution of ester **5b** (10 mg; 0.1 mmol) and iodine (39 mg; 0.3 mmol; 3 eq) in dry dichloromethane (2 mL) was stirred at 0 °C for 1h. The reaction mixture was diluted with dichloromethane and washed with 10% $Na_2S_2O_3$. The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under

reduced pressure. The crude product was purified by crystallization from ethyl acetate, to afford 15 mg (51%) of the iodolactone **14**, as white crystals.

mp > 100 °C (decomposition).

^{1}H NMR (200 MHz, $CDCl_3$): 6.02-5.96 (m, 1H), 5.74-5.67 (m, 1H), 4.09 (dd, J_1=13.0, J_2=6.2, 1H), 3.55 (dd, J_1=10.8, J_2=5.6, 1H), 3.44 (dd, J_1=10.6, J_2=5.8, 1H), 2.82-2.72 (m, 1H),2.53 (s, 1H, OH), 2.40-2.24 (m, 1H), 2.15-2.01 (m, 1H), 1.97-1.75 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): 177.7 (C), 129.9 (CH), 121.7 (CH), 81.9 (CH), 73.6 (C), 47.6 (CH), 27.8 (CH_2), 20.4 (CH_2), 4.8 (CH_2).

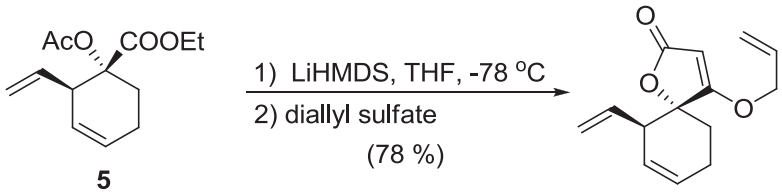
HRMS (ESI): calcd. for $C_9H_{12}IO_3$ $[M+H]^+$: 294.9826; found 294.9819.

IR_{KBr}: 3421, 3033, 2928, 2898, 1764, 1414, 1364, 1315, 1278, 1230, 1202, 1082, 1103, 975.

Elemental analysis: calcd for $C_9H_{11}IO_3$: C 36.76%, H 3.77%; found: C 36.83%, H, 3.87%.

X-ray:

2.18 4-(allyloxy)-6-vinyl-1-oxaspiro[4,5]deca-3,7-dien-2-one (15)



5 **15**

n-Butyl lithium (0.34 mL; 1.5 M, 0.5 mmol; 2 eq) was added to a cold (-20 °C) solution of hexamethyldisilazane (81 mg; 0.5 mmol; 2 eq) in dry THF (4 mL), under argon. After stirring at 0 °C for 20 min, the reaction mixture was cooled down to -80 °C and a solution of ethyl-1-acetoxy-2-vinylcyclohexane-carboxylate **5** (60 mg; 0.25 mmol) in dry THF (0.2 mL) was added. Diallyl sulfate (134 mg; 115 µL; 0.75 mmol; 3 eq) was added after 30 minutes and the reaction mixture was stirred 2h at room temperature. The mixture was partitioned between ethyl acetate and saturated ammonium chloride, the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=4/1), to afford 46 mg (78%) of the pure product **15**, as a colorless oil.

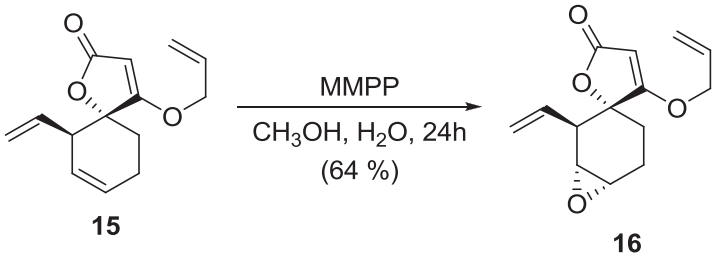
^{1}H NMR (200 MHz, $CDCl_3$): 6.01-5.78 (m, 2H), 5.73-5.50 (m, 2H), 5.43-5.30 (m, 2H), 5.18-5.08 (m, 2H), 5.00 (s, 1H), 4.48-4.45 (m, 2H), 3.16-3.11 (m, 1H), 2.38-2.29 (m, 2H), 2.03-1.96 (t, *J*=6.2, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): 183.5 (C), 177.9 (C), 135.1 (CH), 130.4 (CH), 127.0 (CH), 125.9 (CH), 119.2 (CH_2), 118.0 (CH_2), 89.7 (CH), 84.3 (C), 72.7 (CH_2), 47.3 (CH), 29.1 (CH_2), 23.1 (CH_2).

HRMS (ESI): calcd. for $C_{14}H_{17}O_3$ $[M+H]^+$: 233.1172; found 233.1175.

IR$_{film}$: 3027, 2928, 1754, 1623, 1325, 1283, 1211, 1175, 1054, 927.

2.19 3'-(allyloxy)-2-vinyl-5'*H*-7-oxaspiro[bicyclo[4.1.0]heptane-3,2'-furan]-5'-one (16)



15 **16**

To a solution of spirotetronate **15** (50 mg; 0.22 mmol) in methanol (2.5 mL) and water (1 mL) was added magnesium monoperoxyphthalate (200 mg; 80% MMPP; 0.27 mmol; 1.2 eq) and the mixture was stirred 24h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=7/3), yielding 34 mg (64%) of the epoxide **16**, as colorless crystals.

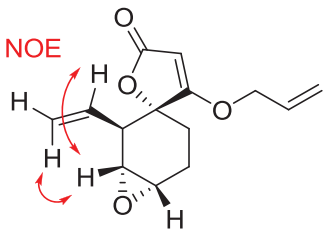
mp 96 °C.

^{1}H NMR (500 MHz, $CDCl_3$): 6.00-5.93 (m, 1H), 5.53 (ddd, J_1=17.0, J_2=10.0, J_3=9.0, 1H), 5.44-5.39 (m, 2H), 5.31-5.27 (m, 1H), 5.24-5.21 (m, 1H), 5.02 (s, 1H), 4.56-4.46 (m, 2H), 3.28-3.27 (m, 1H), 3.11 (d, J=3.5, 1H), 2.97 (d, J=9.5, 1H), 2.27-2.23 (m, 2H), 2.17-2.11 (m, 1H), 1.64-1.60 (m, 1H).

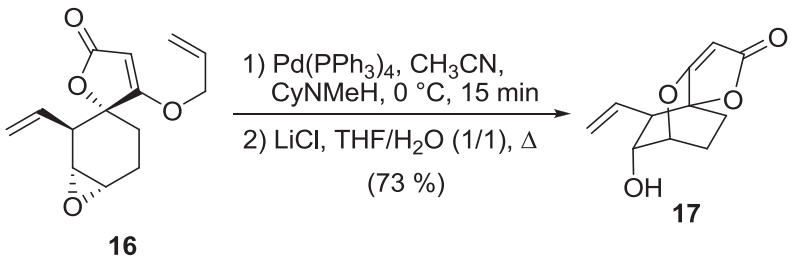
^{13}C NMR (125 MHz, $CDCl_3$): 181.9 (C), 171.0 (C), 131.9 (CH), 130.2 (CH), 120.8 (CH_2), 119.9 (CH_2), 90.9 (CH), 83.1 (C), 73.1 (CH_2), 54.2 (CH), 52.9 (CH), 46.4 (CH), 28.2 (CH_2), 21.7 (CH_2).

HRMS (ESI): calcd. for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1121; found 249.1121.

IR$_{KBr}$: 2923, 1751, 1625, 1336, 1282, 1240, 1224, 1180, 1051, 914.



2.20 8-vinyl-6,7-dihydro-9-(hydroxy)-5H-5,7a-ethano-2H-furo[3,2-b]pyran-2-one (17)



16 **17**

Cyclohexylmethylamine (10.5 mg; 0.093 mmol; 1 eq) was added to a solution of epoxide **16** (23 mg; 0.093 mmol) and $Pd(PPh_3)_4$ (5.3 mg; 4.6 μmol; 5 mol%) in dry acetonitrile (3 mL), at 0 °C. After 15 min of stirring, the solvent was removed on rotovap and the residue was redissolved in THF (4 mL). Lithium chloride (19.5 mg; 0.47 mmol; 5 eq) and water (2 mL) were added and the mixture was heated under reflux for 1h. The product was extracted with ethyl acetate, the organic layer was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=3/2), to afford 14 mg (73%) of the tricyclic alcohol **17**, as a colorless solid.

mp 114 °C.

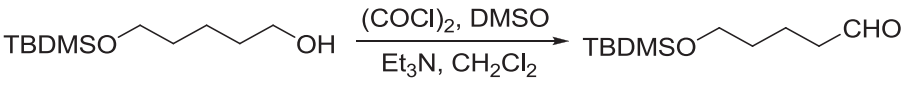
^{1}H NMR (500 MHz, $CDCl_3$): 5.47 (ddd, J_1=17.0, J_2=10.5, J_3=9.0, 1H), 5.27-5.22 (m, 2H), 5.00 (s, 1H), 4.55-4.54 (m, 1H), 4.03 (bs, 1H), 2.69 (dd, J_1=9.0, J_2=4.5, 1H), 2.60 (bs, 1H, OH), 2.43-2.33 (m, 2H), 2.09-2.03 (m, 1H), 1.74-1.69 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): 181.0 (C), 173.2 (C), 132.4 (CH), 120.0 (CH_2), 86.5 (CH), 78.5 (C), 77.1 (CH), 72.2 (CH), 52.4 (CH), 28.4 (CH_2), 19.6 (CH_2).

HRMS (ESI): calcd. for $C_{11}H_{13}O_4$ $[M+H]^+$: 209.0808; found 209.0800.

IR_{KBr}: 3283, 3124, 2923, 1734, 1642, 1399, 1258, 1211, 1180, 1049, 913.

2.21 5-(*tert*-butyldimethylsilyloxy)pentanal[11] (18)



18

DMSO (0.82 mL; 11.6 mmol; 2 eq) was added to a cold (-78 °C) solution of oxalyl chloride (0.5 mL; 5.8 mmol; 1 eq) in dry dichloromethane (10 mL). After 5 min of stirring, a solution of 5-(*tert*-butyldimethylsilyloxy)-pentan-1-ol (1.26 g; 5.8 mmol) in dry dichloromethane (1.5 mL) was added and stirring was continued for 15 min at -70 °C. Triethylamine was added (4.0 mL; 28.9 mmol; 5 eq) at -70 °C and after 10 min the cooling bath was removed. After 45 min, the reaction mixture was distributed between water and dichloromethane, the organic extract was dried over anhydrous $MgSO_4$, evaporated

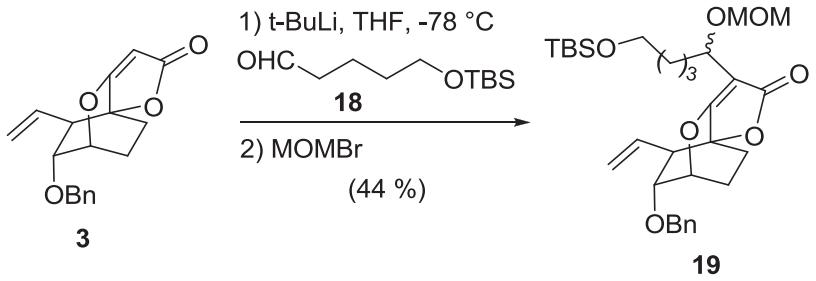
and concentrated. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=9/1), to give 1.1 g (91%) of the aldehyde **18**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): 9.76 (t, *J*=1.8, 1H), 3.62 (t, *J*=6.2, 2H), 2.45 (dt, *J*=7.3, *J*=1.6 2H), 1.75-1.65 (m, 2H), 1.59-1.50 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H);

^{13}C NMR (50 MHz, $CDCl_3$): 202.7 (C), 62.5 (CH_2), 43.6 (CH_2), 32.1 (CH_2), 25.9 (CH_3), 18.6 (CH_2), 18.3 (C), -5.4 (CH_3).

IR_{film}: 2945, 1735.

2.22 9-benzyloxy-3-[5-(tert-butyldimethylsilyloxy)-1-(methoxymethoxy)pentyl]-6,7-dihydro-7-vinyl-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (19)



A solution of t-butyl lithium (0.46 mL; 1.5 M in pentane; 0.46 mmol; 1.5 eq) was added to a cold (-78 °C) solution of **3** (92 mg; 0.31 mmol) in dry THF (5 mL), under argon. The solution was stirred for 30 min before aldehyde **18** (99 mg; 0.46 mmol; 1.5 eq) was added. After 1h of stirring, DIPEA (40 mg; 0.31 mmol; 0.67 eq) and MOMBr (78 mg; 0.62 mmol; 1.35 eq) were added and stirring was continued for 1h at -40 °C. The reaction was quenched with saturated $NaHCO_3$ and the product was extracted with ethyl acetate. The organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=4/1), to afford 76 mg (44%) of diastereoisomeric MOM-protected alcohols **19** (inseparable mixture), as a colorless oil.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Diastereoisomer 1

^{1}H NMR (500 MHz, $CDCl_3$): 7.37-7.28 (m, 5H), 5.51-5.44 (m, 1H), 5.24-5.20 (m, 2H), 4.65 (d, *J*=12.0, 1H), 4.64-4.54 (m, 3H), 4.51 (d, *J*=11.5, 1H), 4.40-4.35 (m, 1H), 3.84-3.81 (m, 1H), 3.59 (t, *J*=6.0, 2H), 3.36 (s, 3H,), 2.85 (dd, J_1=8.5, J_2=4.0, 1H), 2.40-2.32 (m, 2H), 2.10-1.97 (m, 1H), 1.93-1.83 (m, 1H), 1.80-1.64 (m, 2H), 1.57-1.50 (m, 2H), 1.50-1.40 (m, 1H), 1.39-1.30 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 176.2 (C), 171.9 (C), 137.0 (C), 133.0 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 119.9 (CH_2), 99.5 (C), 94.9 (CH_2), 77.7 (CH), 75.2 (CH), 71.6 (CH_2), 69.2 (CH), 63.1

(CH_2), 55.6 (CH_3), 50.4 (CH), 33.5 (CH_2), 32.5 (CH_2), 28.4 (CH_2), 25.9 (CH_3), 22.3 (CH_2), 20.3 (CH_2), 18.3 (C), -5.3 (CH_3).

Diastereoisomer 2

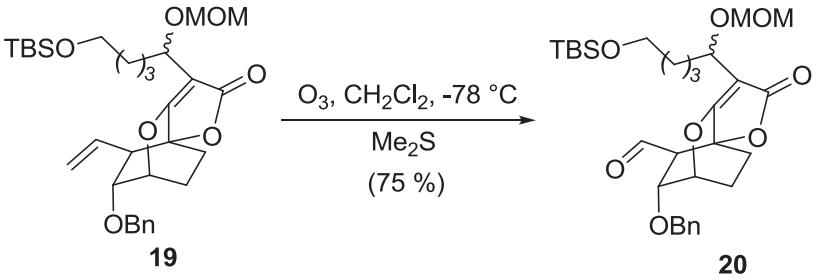
^{1}H NMR (500 MHz, $CDCl_3$): 7.37-7.28 (m, 5H), 5.51-5.44 (m, 1H), 5.24-5.20 (m, 2H), 4.65 (d, *J*=12.0, 1H), 4.64-4.54 (m, 3H), 4.51 (d, *J*=11.5, 1H), 4.40-4.35 (m, 1H), 3.84-3.81 (m, 1H), 3.59 (t, *J*=6.0, 2H), 3.35 (s, 3H), 2.85 (dd, J_1=8.5, J_2=4.0, 1H), 2.40-2.32 (m, 2H), 2.10-1.97 (m, 1H), 1.93-1.83 (m, 1H), 1.80-1.64 (m, 2H), 1.57-1.50 (m, 2H), 1.50-1.40 (m, 1H), 1.39-1.30 (m, 1H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 176.4 (C), 171.9 (C), 137.0 (C), 133.0 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 119.9 (CH_2), 99.3 (C), 94.7 (CH_2), 77.6 (CH), 75.2 (CH), 71.6 (CH_2), 68.9 (CH), 63.1 (CH_2), 55.6 (CH_3), 50.4 (CH), 33.3 (CH_2), 32.5 (CH_2), 28.4 (CH_2), 25.9 (CH_3), 22.2 (CH_2), 20.3 (CH_2), 18.3 (C), -5.3 (CH_3).

HRMS (ESI): calcd. for $C_{31}H_{46}O_7SiNa$ $[M+Na]^+$: 581.2905; found 581.2885.

IR_{film}: 2932, 2958, 1759, 1683, 1651, 1459, 1405, 1252, 1096, 1070, 1035, 924.

2.23 6-benzyloxy-3-[5-(tert-butyldimethylsilyloxy)-1-(methoxymethoxy)pentyl]-6,7-dihydro-7-formyl-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (20)



Ozone was bubbled through a cold (-78 °C) solution of compound **19** (50 mg; 0.09 mmol) in dichloromethane (20 mL). As soon as blue color of dissolved ozone was detected, argon was bubbled through the reaction mixture for 10 min and dimethylsulfide (0.5 mL) was added. The reaction mixture was stirred at room temperature for 5h, volatiles were removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate=7/3), to yield 37.6 mg (75%) of the aldehyde **20** (inseparable mixture of diastereoisomers), as a colorless oil.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Diastereoisomer 1

^{1}H NMR (500 MHz, $CDCl_3$): 9.62 (d, *J*=0.5, 1H), 7.38-7.28 (m, 5H), 4.66-4.63 (m, 1H), 4.59-4.54 (m, 3H), 4.50 (d, *J*=12.0, 1H), 4.40-4.36 (m, 1H), 4.35-4.31 (m, 1H), 3.61-3.58 (m, 2H), 3.34 (s, 3H), 3.19-

3.17 (m, 1H), 2.51-2.45 (m, 1H), 2.39-2.33 (m, 1H), 2.10-2.00 (m, 1H), 1.90-1.82 (m, 1H), 1.75-1.60 (m, 2H), 1.54-1.47 (m, 2H), 1.47-1.25 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 197.4 (CH), 175.9 (C), 170.8 (C), 136.6 (C), 128.6 (CH), 128.4 (CH), 127.9 (CH), 99.2 (C), 95.0 (CH_2), 76.3 (C), 74.9 (CH), 72.2 (CH_2), 71.7 (CH), 68.9 (CH), 63.1 (CH_2), 56.7 (CH), 55.7 (CH_3), 33.1 (CH_2), 32.5 (CH_2), 29.1 (CH_2), 26.0 (CH_3), 22.1 (CH_2), 20.0 (CH_2), 18.3 (C), -5.3 (CH_3).

Diastereoisomer 2

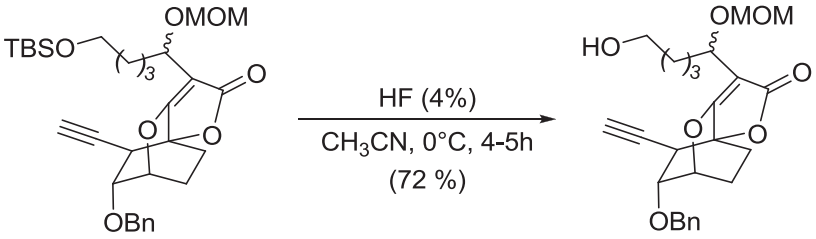
^{1}H NMR (500 MHz, $CDCl_3$): 9.63 (d, *J*=0.5, 1H), 7.38-7.28 (m, 5H), 4.66-4.63 (m, 1H), 4.59-4.54 (m, 3H), 4.50 (d, *J*=12.0, 1H), 4.40-4.36 (m, 1H), 4.35-4.31 (m, 1H), 3.61-3.58 (m, 2H), 3.33 (s, 3H), 3.19-3.17 (m, 1H), 2.51-2.45 (m, 1H), 2.39-2.33 (m, 1H), 2.10-2.00 (m, 1H), 1.90-1.82 (m, 1H), 1.75-1.60 (m, 2H), 1.54-1.47 (m, 2H), 1.47-1.25 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): 197.5 (CH), 175.9 (C), 170.8 (C), 136.6 (C), 128.6 (CH), 128.4 (CH), 127.9 (CH), 99.2 (C), 94.9 (CH_2), 76.4 (C), 74.9 (CH), 72.2 (CH_2), 71.7 (CH), 68.8 (CH), 63.1 (CH_2), 56.7 (CH), 55.7 (CH_3), 33.3 (CH_2), 32.5 (CH_2), 29.1 (CH_2), 26.0 (CH_3), 22.1 (CH_2), 20.0 (CH_2), 18.3 (C), -5.3 (CH_3).

HRMS (ESI): calcd. for $C_{30}H_{44}O_8SiNa$ $[M+Na]^+$: 583.2698; found 583.2693.

IR_{film}: 2952, 2860, 1768, 1726, 1689, 1465, 1410, 1254, 1102, 1038, 929.

2.24 6-benzyloxy-3-[5-hydroxy-1-(methoxymethoxy)pentyl]-6,7-dihidro-7-ethynyl-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (21)



25 **21**

A solution of silyl ether **25** (24 mg; 0.043 mmol) and hydrofluoric acid (4%; 0.12 mL) in acetonitrile (1 mL) was stirred at 0 °C for 6h. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated on rotovap. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=1/1), to afford 13.8 mg (72%) of diastereomeric alcohols **21**, as a colorless oil.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Diastereoisomer 1

^{1}H NMR (500 MHz, $CDCl_3$): 7.39-7.33 (m, 5H), 4.76 (d, *J*=11.5, 1H), 4.68 (d, *J*=7.0, 1H), 4.60-4.55 (m, 3H), 4.47-4.43 (m, 1H), 4.05-4.01 (m, 1H), 3.64-3.61 (m, 2H), 3.37 (s, 3H), 3.13-3.12 (m, 1H), 2.37-2.26 (m, 3H), 2.08-2.00 (m, 1H), 1.97-1.79 (m, 2H), 1.77-1.71 (m, 1H), 1.61-1.57 (m, 2H), 1.55-1.37 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): 175.2 (C), 171.8 (C), 136.6 (C), 128.6 (CH), 128.3 (CH), 127.9 (CH), 99.7 (C), 94.7 (CH_2), 79.4 (C or CH), 79.3 (C or CH), 75.6 (C), 74.8 (CH), 73.7 (CH), 71.8 (CH_2), 68.8 (CH), 62.7 (CH_2), 55.6 (CH_3), 40.4 (CH), 33.1 (CH_2), 32.4 (CH_2), 27.1 (CH_2), 21.8 (CH_2), 20.1 (CH_2).

Diastereoisomer 2

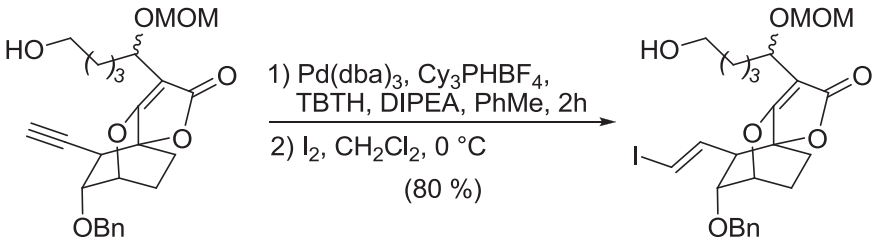
^{1}H NMR (500 MHz, $CDCl_3$): 7.39-7.33 (m, 5H), 4.76 (d, *J*=11.5, 1H), 4.67 (d, *J*=7.0, 1H), 4.60-4.55 (m, 3H), 4.47-4.43 (m, 1H), 4.05-4.01 (m, 1H), 3.64-3.61 (m, 2H), 3.36 (s, 3H), 3.13-3.12 (m, 1H), 2.37-2.26 (m, 3H), 2.08-2.00 (m, 1H), 1.97-1.79 (m, 2H), 1.77-1.71 (m, 1H), 1.61-1.57 (m, 2H), 1.55-1.37 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): 175.2 (C), 171.7 (C), 136.6 (C), 128.6 (CH), 128.3 (CH), 127.9 (CH), 99.6 (C), 94.4 (CH_2), 79.4 (C or CH), 79.3 (C or CH), 75.6 (C), 74.8 (CH), 73.7 (CH), 71.8 (CH_2), 68.4 (CH), 62.6 (CH_2), 55.7 (CH_3), 40.4 (CH), 33.2 (CH_2), 32.3 (CH_2), 27.1 (CH_2), 21.8 (CH_2), 20.1 (CH_2).

HRMS (ESI): calcd. for $C_{25}H_{31}O_7$ $[M+H]^+$: 443.2064; found 443.2062.

IR$_{film}$: 3483, 3281, 2923, 2853, 2108, 1757, 1684, 1459, 1411, 1075, 1033.

2.25 6-benzyloxy-6,7-dihydro-7-(*E*-2-iodovinyl)-3-[5-hydroxy-1-(methoxymethoxy)pentyl]-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (22)



A mixture of tricyclohexylphosphonium tetrafluoroborate (1 mg; 2.7 μmol; 5 mol%), $Pd_2(dba)_3$ (0.62 mg; 0.68 μmol; 1.25 mol%), DIPEA (0.7 mg; 0.05 mmol; 36 mol%) and toluene (1 mL) was stirred at room temperature for 10 min and a solution of acetylene **21** (60 mg; 0.14 mmol) in toluene (0.5 mL) was added dropwise over 5 minutes, followed by the addition of TBTH (47.5 mg; 0.16 mmol; 1.15 eq), dissolved in toluene (0.5 mL). After 2 h of stirring, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in dry dichloromethane (1 mL). The resulted solution was treated with a solution of iodine (172 mg; 1.36 mmol; 10 eq) in dry dichloromethane (1.5 mL). After 15 minutes the product was extracted with ethyl acetate, the extract was washed with saturated $NaHCO_3$, 10%

$Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$, filtered and concentrated on rotovap. The residue was purified by column chromatography (petroleum ether/ethyl acetate=1/1), yielding 62 mg (80%) of the vinyl iodide **22**, as a mixture of diastereoisomers.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Diastereoisomer 1:

^{1}H NMR (500 MHz, $CDCl_3$): 7.40-7.25 (m, 5H), 6.28 (d, *J*=14.5, 1H), 6.16-6.09 (m, 1H), 4.64-4.59 (m, 4H), 4.54 (d, *J*=12.0, 1H), 4.39 (t, *J*=7.0, 1H), 3.81-3.77 (m, 1H), 3.67-3.63 (m, 2H), 3.37 (s, 3H), 2.84 (dd, J_1=8.5, J_2=3.5, 1H), 2.38-2.29 (m, 2H), 2.05-1.97 (m, 1H), 1.94-1.73 (m, 2H), 1.70-1.66 (m, 1H), 1.66-1.54 (m, 3H), 1.53-1.30 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): 175.6 (C), 171.5 (C), 140.2 (CH), 136.7 (C), 128.7 (CH), 128.4 (CH), 127.9 (CH), 99.8 (C), 95.1 (CH_2), 81.0 (CH), 77.3 (CH), 76.1 (C), 75.1 (CH), 72.0 (CH_2), 69.4 (CH), 62.7 (CH_2), 55.8 (CH_3), 52.5 (CH), 33.4 (CH_2), 32.3 (CH_2), 28.3 (CH_2), 21.9 (CH_2), 20.2 (CH_2).

Diastereoisomer 2:

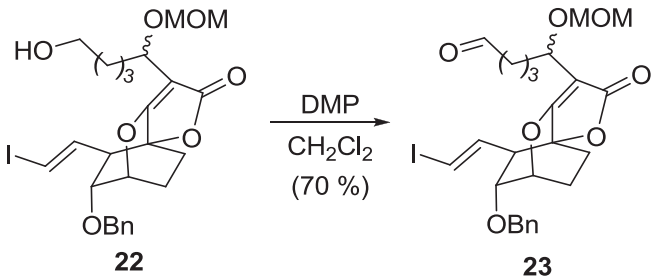
^{1}H NMR (500 MHz, $CDCl_3$): 7.40-7.25 (m, 5H), 6.28 (d, *J*=14.5, 1H), 6.16-6.09 (m, 1H), 4.64-4.59 (m, 4H), 4.54 (d, *J*=12.0, 1H), 4.39 (t, *J*=7.0, 1H), 3.81-3.77 (m, 1H), 3.67-3.63 (m, 2H), 3.36 (s, 3H), 2.84 (dd, J_1=8.5, J_2=3.5, 1H), 2.38-2.29 (m, 2H), 2.05-1.97 (m, 1H), 1.94-1.73 (m, 2H), 1.70-1.66 (m, 1H), 1.66-1.54 (m, 3H), 1.53-1.30 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): 176.2 (C), 171.5 (C), 140.2 (CH), 136.7 (C), 128.7 (CH), 128.4 (CH), 127.9 (CH), 99.6 (C), 95.1 (CH_2), 81.0 (CH), 77.3 (CH), 76.1 (C), 75.1 (CH), 72.0 (CH_2), 68.8 (CH), 62.7 (CH_2), 55.8 (CH_3), 52.5 (CH), 32.8 (CH_2), 32.3 (CH_2), 28.2 (CH_2), 22.0 (CH_2), 20.2 (CH_2).

HRMS (ESI): calcd. for $C_{25}H_{32}IO_7$ $[M+H]^+$: 571.1187; found 571.1183.

IR_{film}: 3473, 2927, 2856, 1756, 1682, 1459, 1412, 1094, 1073, 1035, 920.

2.26 6-benzyloxy-6,7-dihydro-7-(*E*-2-iodovinyl)-3-[1-(methoxymethoxy)-5-oxopentyl]-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (23)



22 **23**

DMP (19 mg; 0.045 mmol; 2 eq) was added to a solution of alcohol **22** (12.8 mg; 0.0225 mmol) in dry dichloromethane (1 mL) and the reaction mixture was stirred at room temperature for 15 minutes. The mixture was diluted with dichloromethane, washed with 10% $Na_2S_2O_3$ and saturated $NaHCO_3$, and dried over anhydrous $MgSO_4$. The solvent was removed on rotovap and the residue was purified by column chromatography (petroleum ether/ethyl acetate=1/1), to give 9 mg (70%) of the aldehyde **23**, as a colorless oil.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^1H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Diastereoisomer 1:

^{1}H NMR (500 MHz, $CDCl_3$): 9.78 (bt, *J*=1.5, 1H), 7.41-7.26 (m, 5H), 6.28 (d, *J*=14.5, 1H), 6.16-6.09 (m, 1H), 4.64-4.52 (m, 5H), 4.40-4.37 (m, 1H), 3.84-3.77 (m, 1H), 3.37 (s, 3H), 2.84 (dd, J_1=9.0, J_2=3.5, 1H), 2.52-2.48 (m, 2H), 2.38-2.30 (m, 2H), 2.08-1.98 (m, 1H), 1.97-1.86 (m, 1H), 1.85-1.60 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): 202.1 (CH), 175.8 (C), 171.4 (C), 140.1 (CH), 136.7 (C), 128.7 (CH), 128.4 (CH), 127.9 (CH), 99.4 (C), 95.1 (CH_2), 81.0 (CH), 77.2 (CH), 76.2 (C), 75.2 (CH), 72.0 (CH_2), 69.1 (CH), 55.8 (CH_3), 52.5 (CH), 43.4 (CH_2), 33.1 (CH_2), 28.3 (CH_2), 20.2 (CH_2), 18.4 (CH_2).

Diastereoisomer 2:

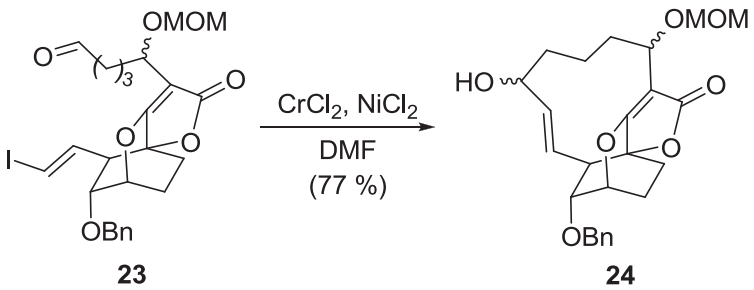
^{1}H NMR (500 MHz, $CDCl_3$): 9.77 (bt, *J*=1.5, 1H), 7.41-7.26 (m, 5H), 6.28 (d, *J*=14.5, 1H), 6.16-6.09 (m, 1H), 4.64-4.52 (m, 5H), 4.40-4.37 (m, 1H), 3.84-3.77 (m, 1H), 3.36 (s, 3H), 2.84 (dd, J_1=9.0, J_2=3.5, 1H), 2.52-2.48 (m, 2H), 2.38-2.30 (m, 2H), 2.08-1.98 (m, 1H), 1.97-1.86 (m, 1H), 1.85-1.60 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): 202.1 (CH), 176.3 (C), 171.5 (C), 140.1 (CH), 136.7 (C), 128.7 (CH), 128.4 (CH), 127.9 (CH), 99.3 (C), 95.2 (CH_2), 81.0 (CH), 77.2 (CH), 76.2 (C), 75.2 (CH), 72.0 (CH_2), 68.5 (CH), 55.8 (CH_3), 52.5 (CH), 43.4 (CH_2), 32.6 (CH_2), 28.2 (CH_2), 20.2 (CH_2), 18.4 (CH_2).

HRMS (ESI): calcd. for $C_{25}H_{29}IO_7K$ $[M+K]^+$: 607.0589; found 607.0576.

IR_{film}: 2931, 2859, 1759, 1685, 1461, 1413, 1100, 1038.

2.27 11-benzyloxy-5,6,7,8,11,12,13,14-octahydro-8-hydroxy-4-(methoxymethoxy)-12,14a,3-(epoxymethino)-2H-1-benzoxacyclododecyn-2-2(4H,10aH)-one (24)



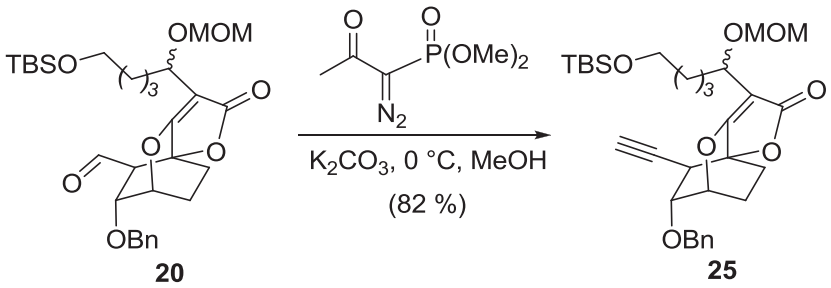
23 **24**

A suspension of vinyl iodide **23** (9 mg; 0.016 mmol), $CrCl_2$ (33.1 mg; 0.272 mmol; 17 eq) and $NiCl_2$ (1 mg) in a freshly distilled DMF (1.5 mL) was stirred 1h at room temperature and then 1.5h at 50 °C, under argon. The reaction mixture was diluted with ethyl acetate and water and the organic extract was washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate=1/2), to afford 5.4 mg (77%) of the tetracyclic product, as an inseparable mixture of four diastereoisomers.

HRMS (ESI): calcd. for $C_{25}H_{30}O_7K$ $[M+K]^+$: 481.1623; found 481.1608.

IR_{film}: 3464, 2930, 2857, 1752, 1681,1462, 1414, 1097,1036.

2.28 6-benzyloxy-3-[5-(tert-butyldimethylsilyloxy)-1-(methoxymethoxy)pentyl]-6,7-dihidro-7-ethynyl-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (25)



Bestmann-Ohira reagent (12.4 mg; 0.064 mmol; 3 eq) and potassium carbonate (14.5 mg; 0.105 mmol; 5 eq) were added to cold (0 °C) solution of aldehyde **20** (12 mg; 0.021 mmol) in dry methanol (1 mL) and the mixture was stirred at room temperature for 2h. The solvent was removed under reduced pressure and the product was extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by dry-flash chromatography (petroleum ether/ethyl acetate=7/3), to yield 9.8 mg (82%) of the acetylene **25** (inseparable mixture of diastereoisomers), as a colorless oil.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^1H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Diastereoisomer 1:

^1H NMR (500 MHz, $CDCl_3$): 7.39-7.31 (m, 5H), 4.76 (d, *J*=11.5, 1H), 4.68 (d, *J*=6.5, 1H), 4.60-4.54 (m, 3H), 4.46-4.41 (m, 1H), 4.04-4.02 (m, 1H), 3.59 (dt, J_1=6.0, J_2=2.0, 2H), 3.36 (s, 3H), 3.12 (dd, J_1=6.0, J_2=2.5, 1H), 2.34-2.23 (m, 2H), 2.23 (d, *J*=2.5, 1H), 2.08-1.97 (m, 1H), 1.95-1.85 (m, 1H), 1.83-1.67 (m, 2H), 1.56-1.30 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 175.1 (C), 171.7 (C), 136.6 (C), 128.6 (CH), 128.3 (CH), 127.9 (CH), 99.8 (C), 94.7 (CH_2), 79.3 (C or CH), 79.2 (C or CH), 75.5 (C), 74.8 (CH), 73.6 (CH), 71.8 (CH_2), 68.8 (CH), 63.2 (CH_2), 55.6 (CH_3), 40.4 (CH), 33.3 (CH_2), 32.6 (CH_2), 27.1 (CH_2), 26.0 (CH_3), 22.1 (CH_2), 20.1 (CH_2), 18.3 (C), -5.3 (CH_3).

Diastereoisomer 2:

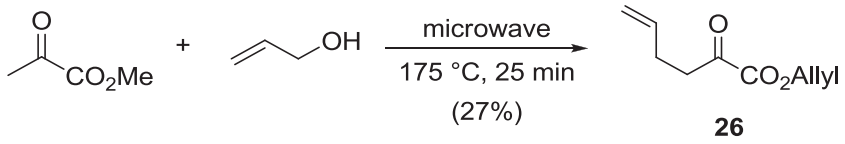
^{1}H NMR (500 MHz, $CDCl_3$): 7.39-7.31 (m, 5H), 4.76 (d, *J*=11.5, 1H), 4.67 (d, *J*=7.0, 1H), 4.60-4.54 (m, 3H), 4.46-4.41 (m, 1H), 4.04-4.02 (m, 1H), 3.59 (dt, J_1=6.0, J_2=2.0, 2H), 3.36 (s, 3H), 3.12 (dd, J_1=6.0, J_2=2.5, 1H), 2.34-2.23 (m, 2H), 2.25 (d, *J*=2.5, 1H), 2.08-1.97 (m, 1H), 1.95-1.85 (m, 1H), 1.83-1.67 (m, 2H), 1.56-1.30 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 175.0 (C), 171.7 (C), 136.6 (C), 128.6 (CH), 128.3 (CH), 127.9 (CH), 99.8 (C), 94.4 (CH_2), 79.3 (C or CH), 79.2 (C or CH), 75.6 (C), 74.8 (CH), 73.6 (CH), 71.8 (CH_2), 68.5 (CH), 63.1 (CH_2), 55.6 (CH_3), 40.4 (CH), 33.6 (CH_2), 32.6 (CH_2), 27.1 (CH_2), 26.0 (CH_3), 22.2 (CH_2), 20.1 (CH_2), 18.3 (C), -5.3 (CH_3).

HRMS (ESI): calcd. for $C_{31}H_{44}O_7SiK$ $[M+K]^+$: 595.2487; found 595.2467.

IR_{film}: 3288, 2931, 2858, 2108, 1764, 1688, 1463, 1409, 1253, 1096, 1033.

2.29 Allyl 2-oxohex-5-enoate (26)



26

A mixture of methyl 2-oxopropanoate (5 mL) and allyl alcohol (2.5 mL) was heated in a microwave oven at 175 °C for 5 minutes. The excess of allyl alcohol was distilled off under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate=1/1), to yield 240 mg (27%) of the pure product, as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): 6.07-5.72 (m, 2H), 5.45-5.29 (m, 2H), 5.12-4.99 (m, 2H), 4.75 (d, *J*=6.0, 2H), 2.96 (t, *J*=7.4, 2H), 2.40 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): 193.3 (C), 160.5 (C), 135.6 (CH), 130.6 (CH), 119.7 (CH_2), 115.8 (CH_2), 66.6 (CH_2), 38.3 (CH_2), 26.7 (CH_2).

IR_{film}: 3081, 2981, 1726, 1643, 1241, 1060, 914.

3 Biological tests

3.1 Antibacterial activity

The agar plate diffusion assay and the determination of MIC values were performed according to the literature procedure.[12] The determination of MIC was modified, with respect to the literature procedure, in that Mueller Hinton broth was used.

3.2 Cytotoxicity assay

Reagents: RPMI-1640 medium was purchased from PAA The Cell Culture Company (Linz, Austria), Fetal calf serum (FCS), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), gentamicin sulfate salt, penicillin, streptomycin, glutamine, β-mercaptoethanol, phytohemagglutinin (PHA), dimethyl sulfoxide (DMSO) and Histopaque were purchased from the Sigma Chemical Co. (St. Louis, MO, USA), 0.22 μm Millipore Ultrafree-MC centrifugal devices were purchased from Merck Millipore (Billerica, Massachusetts, US).

Cell culture. Human cervix adenocarcinoma cells (HeLa), were grown in RPMI-1640 medium supplemented with 10% fetal calf serum (FCS), 1% glutamine (200 mM), 1% penicillin (10000 IU mL^{-1}) and 1% streptomycin (10 mg mL^{-1}). The cells were grown at 37 °C in a 6.0 % CO_2 humidified air atmosphere. Peripheral blood mononuclear cells (PBMC) were separated from whole heparinized blood of healthy volunteer. Blood was diluted with phosphate buffered saline (PBS) (1:1) and layered on Histopaque solution. After centrifugation, interface cells were collected and washed three times with PBS. After counting, cells were resuspended in nutrient medium. Nutrient medium was RPMI-1640 medium, supplemented with 10% fetal calf serum (FCS), 1% glutamine (200 mM), 1% β-mercaptoethanol (5 μM), 1% penicillin (10000 IU mL^{-1}), 1% streptomycin (10 mg mL^{-1}) and with 0,5% phytohemagglutinin (PHA) (1 mg mL^{-1}). The cells were grown at 37 °C in a humidified atmosphere with 6% CO_2.

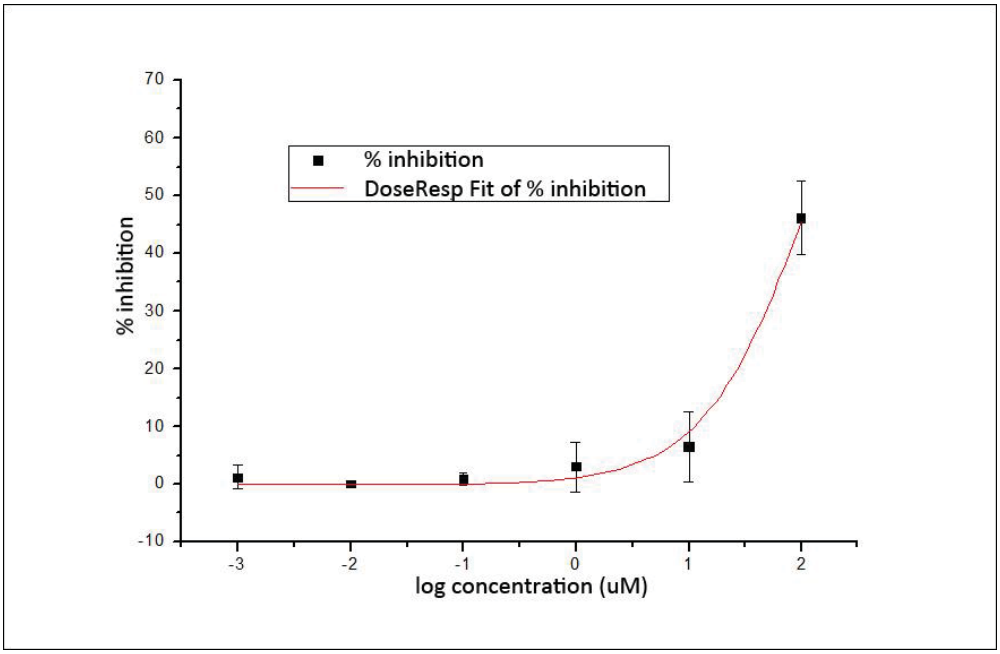
Determination of target cell survival. HeLa cells were seeded (10 000 cells per well) into 96-well microtiter plates and 24 h later, after the cell adherence, six different concentrations of investigated compounds were added to the wells. Final concentrations were in the range from 0.001 μM to 100 μM for HeLa cells and PBMCs. Only nutrient medium was added to the cells in the control wells. All experiments were done in triplicate. Nutrient medium void of cells was used as blank. PBMC were seeded (200,000 cells per well) into nutrient medium in 96-well microtiter plates and 2 h later, investigated compounds were added to the wells, in triplicates, to six final concentrations, except to the control wells where a nutrient medium only was added to the cells. Nutrient medium void of cells was used as blank. Cell survival was determined by MTT test according to the method of Mosmann[13] and modified by Ohno and Abe,[14] 24 and 72 h after the drug addition to HeLa cells and PBMCs, respectively. Briefly, 20 μL of MTT solution (5 mg/mL in PBS) were added to each well and incubated for 4 h at 37 °C in humidified atmosphere with 6% CO_2. After the incubation, medium was carefully removed and 200 μL of DMSO were added to dissolve the formazan complexes; absorbance was read at

492 nm. The *IC*50 value which represents drug concentration that diminishes 50% of viable cells was assessed from the graph of cell survival *vs.* concentration of the investigated compound.

Results of the determination of cytotoxicity of compound 1 on HeLa cells

Compound **1**: IC_{50} = 111.82 μM

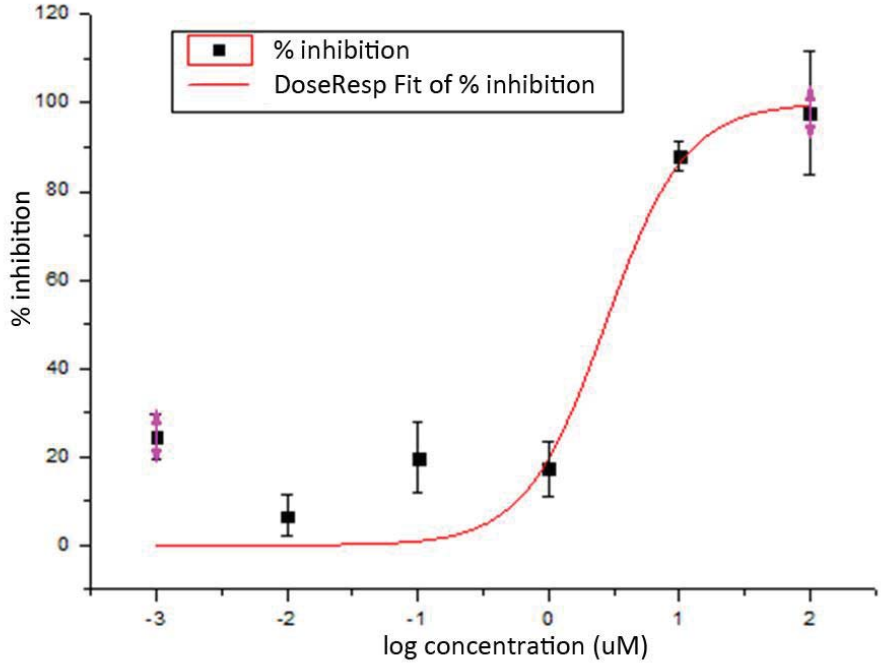
A1		A2		LOGx0		p		IC50	IC90	IC20	IC80
Value	Error	Value	Error	Value	Error	Value	Error	Value			
0	0	100	0	1.97708	0.06242	0.80666	0.1098	94.86	1445.572	17.01039	528.9862
0	0	100	0	2.00369	0.05058	0.88424	0.3346	110.95	1331.318	23.13326	532.1003
0	0	100	0	2.21125	0.01468	0.90804	0.03336	162.65	1828.641	35.3364	748.6541



Results of the determination of cytotoxicity of compound 1 on Peripheral blood mononuclear cells (PBMC)

Compound **1**: IC_{50} = 3.17 μM

A1		A2		LOGx0		p		IC50	IC90	IC20	IC80
Value	Error	Value	Error	Value	Error	Value	Error	Value			
0	0	100	0	0.43459	0.25114	1.41122	0.72	2.72014	12.90544	1.01852	7.26464
0	0	100	0	0.43658	0.18552	1.66093	0.63722	2.7326	10.25882	1.18602	6.29591
0	0	100	0	0.60741	0.37669	1.65371	1.37404	4.04957	15.29113	1.75123	9.36428



4 Computational details

The calculations using the restricted Kohn–Sham formalism have been performed with the Amsterdam Density Functional (ADF) program package, version 2013.01,[15,16,17] with hybrid exchange-correlation functional (B3LYP).[18,19] An all electron Triple-zeta Slater-type orbitals (STO) plus one polarization function (TZP) basis set has been used for all atoms. Conductor like screening solvation model (COSMO), as implemented in ADF, was included in the density functional theory (DFT) geometry optimizations,[20] with water as a solvent. Analytical harmonic frequencies[21,22] were calculated and in all cases the global minimum was confirmed by the absence of imaginary frequency modes. Three types of charge analysis (Hirshfeld,[23] Voronoi Deformation Density (VDD)[24] and Multipole Derived Charges (MDC)[25]) have been performed in order to test the differences in electron density of enone β-position. Electrostatic potential surfaces of *atrop*-abyssomicin C and its desmethyl derivative **1** were computed by mapping electrostatic potential onto surfaces of molecular electron density (0.005 electrons/au^3) and color-coding.

Table S1. Selected dihedral angles (^{o}) and charges on *atrop*-abyssomicin C, *atrop*-*O*-benzyl-abyssomicin C and 1, calculated with B3LYP/TZP in VACUUM.

Molecule	Dihedral (C_9=C_8–C_7=O)	Dihedral (C_{10}–C_9=C_8–C_7)	Atom	Hirshfeld	VDD	MDC-q
atrop-abyssomicin C	24.681	164.645	Cα[1]	-0.0523	-0.088	0.250853
			Cβ	-0.0175	-0.032	0.240496
atrop-*O*-benzyl-abyssomicin C	25.176	164.859	Cα	-0.0534	-0.086	0.257243
			Cβ	-0.0170	-0.033	0.238229
1	26.618	167.118	Cα	-0.0531	-0.087	0.250531
			Cβ	-0.0160	-0.032	0.245859

Table S2. Selected dihedral angles (^{o}) and charges on *atrop*-abyssomicin C, *atrop*-*O*-benzylabyssomicin C and 1, calculated with B3LYP/TZP in COSMO.

Molecule	Dihedral (C_9=C_8–C_7=O)	Dihedral (C_{10}–C_9=C_8–C_7)	Atom	Hirshfeld	VDD	MDC-q
atrop-abyssomicin C	23.665	162.289	Cα	-0.0524	-0.088	0.240093
			Cβ	-0.0052	-0.018	0.259761
atrop-*O*-benzyl-abyssomicin C	24.555	163.387	Cα	-0.0520	-0.089	0.231851
			Cβ	-0.0073	-0.024	0.252047
1	27.687	166.154	Cα	-0.0499	-0.088	0.237196
			Cβ	-0.0083	-0.025	0.259583

[1] Cα is C_9 and Cβ is C_8

Coordinates of optimized structures

abyssomicin C
VACUUM

Total energy = -7619.33 kcal/mol

O	1.529938	-0.623388	-1.301535
O	0.852753	-0.470565	2.165271
O	-1.069169	-1.598909	2.536861
O	3.468105	2.379969	-0.505467
H	3.220997	3.311834	-0.463350
O	-0.953873	-2.647092	-1.572654
O	-2.780465	3.208577	-0.962835
C	2.729710	0.220708	-1.195700
H	3.104598	0.290068	-2.212692
C	3.748021	-0.426429	-0.247946
H	4.597997	0.254853	-0.219367
C	3.101228	-0.493686	1.165761
H	3.152399	-1.503974	1.571656
H	3.594333	0.176702	1.870660
C	1.626760	-0.103199	1.034018
C	0.988282	-0.827824	-0.107023
C	-0.150418	-1.439793	0.285671
C	-0.244911	-1.232186	1.742935
C	2.281130	1.601730	-0.675769
H	1.649154	2.056857	-1.436079
C	1.483996	1.416726	0.648877
H	1.976358	1.993750	1.435711
C	-1.224804	-1.984264	-0.589735
C	-2.655705	-1.530350	-0.279218
H	-2.760861	-1.475523	0.804511
C	-2.834181	-0.092269	-0.879242
H	-2.020760	0.103087	-1.583862
H	-3.744607	-0.079542	-1.483312
C	-2.937448	1.071048	0.159078
H	-2.400062	0.763009	1.057958
C	-2.204932	2.283703	-0.420975
C	-0.705991	2.219953	-0.422828
H	-0.257863	2.568607	-1.346816
C	0.015359	1.754820	0.595250
H	-0.507402	1.486474	1.506369
C	4.218762	-1.792143	-0.750823
H	3.393061	-2.502895	-0.813055
H	4.967384	-2.203272	-0.071552
H	4.672468	-1.712190	-1.740508
C	-3.678447	-2.524982	-0.829943
H	-3.587984	-2.623077	-1.911273
H	-4.689655	-2.191198	-0.592138
H	-3.532658	-3.513571	-0.392416
C	-4.384909	1.386281	0.530357
H	-4.436898	2.154047	1.303609
H	-4.882923	0.490703	0.906030
H	-4.932983	1.751648	-0.338116

abyssomicin C
COSMO

Total energy = -7640.86 kcal/mol

O	1.530331	-0.643583	-1.291194
O	0.841837	-0.485502	2.165200
O	-1.041617	-1.649449	2.553958
O	3.443285	2.391652	-0.513267
H	3.170716	3.319618	-0.490123
O	-0.952699	-2.598980	-1.596872
O	-2.783613	3.214196	-0.980640
C	2.739753	0.216617	-1.194936
H	3.105441	0.275959	-2.213220
C	3.749384	-0.426590	-0.239852
H	4.598704	0.254006	-0.211441
C	3.102214	-0.487188	1.173897
H	3.160521	-1.494331	1.584411
H	3.586004	0.193903	1.873070
C	1.627648	-0.105054	1.032727
C	0.993439	-0.834320	-0.103271
C	-0.153562	-1.446951	0.292906
C	-0.230556	-1.251462	1.743905
C	2.270828	1.593595	-0.684589
H	1.639153	2.037040	-1.448707
C	1.471800	1.411284	0.641326
H	1.952002	1.995800	1.427991
C	-1.225979	-1.962948	-0.584630
C	-2.652919	-1.519790	-0.272662
H	-2.754281	-1.453988	0.809905
C	-2.835148	-0.083634	-0.883243
H	-2.025564	0.110564	-1.591657
H	-3.749442	-0.079014	-1.480287
C	-2.934171	1.083638	0.151262
H	-2.389749	0.785974	1.048147
C	-2.197826	2.285731	-0.432293
C	-0.708571	2.228077	-0.435149
H	-0.250000	2.598751	-1.344546
C	0.002789	1.738213	0.580693
H	-0.529135	1.464391	1.483801
C	4.232214	-1.791382	-0.731878
H	3.416515	-2.515693	-0.775068
H	4.990880	-2.181812	-0.052338
H	4.674768	-1.712796	-1.726133
C	-3.683272	-2.515681	-0.806249
H	-3.625486	-2.602902	-1.891037
H	-4.687699	-2.183439	-0.542079
H	-3.525748	-3.505565	-0.375468
C	-4.379197	1.393463	0.533894
H	-4.426765	2.178957	1.289416
H	-4.857789	0.501726	0.941719
H	-4.950738	1.719080	-0.335611

atrop-abyssomicin C
VACUUM

Total energy = -7621.04 kcal/mol

O	1.439992	-0.530220	-1.412644
O	0.999827	-0.719667	2.097778
O	-0.951295	-1.804194	2.471669
O	3.276426	2.515424	-0.594071
H	2.967944	3.406781	-0.389318
O	-1.169712	-2.487790	-1.668073
O	-2.594714	2.393435	1.601507
C	2.617800	0.339827	-1.306685
H	2.919818	0.522827	-2.334056
C	3.726284	-0.348089	-0.498351
H	4.524899	0.389998	-0.415452
C	3.170589	-0.659214	0.923721
H	3.229100	-1.726462	1.139056
H	3.722573	-0.130372	1.701496
C	1.699770	-0.241915	0.959108
C	0.975272	-0.839254	-0.202298
C	-0.151143	-1.457948	0.199628
C	-0.155904	-1.387393	1.675779
C	2.148354	1.642402	-0.636603
H	1.367824	2.079576	-1.260108
C	1.575701	1.320270	0.779519
H	2.239764	1.771688	1.518242
C	-1.312307	-1.847283	-0.644568
C	-2.661428	-1.244634	-0.234415
H	-2.583334	-0.920498	0.803345
C	-2.927837	0.002954	-1.140823
H	-2.070139	0.193158	-1.790162
H	-3.743196	-0.246495	-1.824637
C	-3.318536	1.295157	-0.400488
H	-4.187193	1.097442	0.231494
C	-2.262500	1.864956	0.556273
C	-0.831948	1.747959	0.147285
H	-0.640448	1.508554	-0.891854
C	0.157712	1.752049	1.042626
H	-0.103134	1.940315	2.077933
C	4.269998	-1.591185	-1.204634
H	3.489970	-2.341516	-1.345106
H	5.069043	-2.041896	-0.613757
H	4.679981	-1.339278	-2.184602
C	-3.784514	-2.281867	-0.335131
H	-3.833939	-2.694004	-1.343567
H	-4.745281	-1.820824	-0.097563
H	-3.620914	-3.103531	0.363383
C	-3.699469	2.407774	-1.398162
H	-4.029467	3.303580	-0.871521
H	-4.510527	2.070632	-2.045987
H	-2.853615	2.678411	-2.035576

atrop-abyssomicin C
COSMO

Total energy = -7643.02 kcal/mol

O	1.441193	-0.571285	-1.403657
O	0.979052	-0.703983	2.096853
O	-0.958270	-1.777918	2.491519
O	3.229881	2.530492	-0.650703
H	2.884344	3.420294	-0.492793
O	-1.157896	-2.476263	-1.665870
O	-2.605571	2.272854	1.674931
C	2.624050	0.321353	-1.317329
H	2.916360	0.481609	-2.348808
C	3.726657	-0.349413	-0.492051
H	4.516028	0.397305	-0.407097
C	3.166101	-0.654830	0.930040
H	3.223165	-1.721504	1.145928
H	3.712578	-0.120431	1.705803
C	1.698879	-0.231875	0.952292
C	0.975895	-0.844800	-0.198662
C	-0.162645	-1.455323	0.212845
C	-0.160309	-1.364815	1.676479
C	2.126778	1.627078	-0.673174
H	1.338085	2.032316	-1.303622
C	1.574402	1.327010	0.755977
H	2.244806	1.786260	1.481632
C	-1.314830	-1.836118	-0.632725
C	-2.664992	-1.240031	-0.244813
H	-2.601329	-0.920013	0.794628
C	-2.900342	0.019289	-1.149191
H	-2.024823	0.216264	-1.770491
H	-3.701221	-0.218139	-1.852277
C	-3.302326	1.305817	-0.403739
H	-4.195030	1.108784	0.192626
C	-2.261264	1.835850	0.580044
C	-0.840471	1.781276	0.155896
H	-0.658810	1.602586	-0.895890
C	0.160184	1.751747	1.041326
H	-0.079473	1.898325	2.087815
C	4.299421	-1.589529	-1.179240
H	3.537808	-2.361197	-1.307855
H	5.105348	-2.010766	-0.576905
H	4.704560	-1.338814	-2.160800
C	-3.801003	-2.260429	-0.368571
H	-3.867424	-2.643511	-1.387363
H	-4.751347	-1.787325	-0.116860
H	-3.648682	-3.102622	0.308176
C	-3.630152	2.434853	-1.403946
H	-3.965763	3.331912	-0.882811
H	-4.425575	2.109439	-2.075658
H	-2.759395	2.693747	-2.009998

***O*-benzyl-abyssomicin C**
VACUUM

Total energy = -9800.18 kcal/mol

O	-0.506805	-1.680307	-1.243969
O	-1.246820	-1.240268	2.184670
O	-3.490470	-1.045248	2.379114
O	2.692796	-0.207370	-0.270952
C	3.224072	1.127980	-0.208052
O	-3.704656	-1.860071	-1.758699
O	-1.882602	4.045182	-0.607021
C	0.949232	-1.642378	-1.026540
H	1.375466	-1.772558	-2.016816
C	1.376623	-2.756721	-0.065052
H	2.450148	-2.623327	0.071348
C	0.655334	-2.517250	1.293114
H	1.360672	-2.294406	2.094532
H	0.079068	-3.394147	1.589113
C	-0.313136	-1.346244	1.120184
C	-1.159502	-1.542211	-0.097244
C	-2.469747	-1.385019	0.195272
C	-2.543059	-1.206009	1.656401
C	1.288188	-0.248431	-0.464538
H	1.002707	0.485594	-1.219730
C	0.472686	-0.007838	0.843902
H	1.173096	0.122235	1.672800
C	-3.596343	-1.178336	-0.757844
C	-4.505193	0.027096	-0.483405
H	-4.679675	0.067776	0.592237
C	-3.730832	1.319933	-0.917780
H	-2.860995	1.030903	-1.514601
H	-4.366454	1.895275	-1.595475
C	-3.287219	2.268927	0.239891
H	-3.092847	1.650649	1.118227
C	-1.960084	2.912517	-0.169751
C	-0.759568	2.012845	-0.151129
H	-0.117085	2.123099	-1.017449
C	-0.521794	1.124004	0.811773
H	-1.176238	1.129429	1.675591
C	1.110654	-4.149692	-0.638349
H	1.646892	-4.297099	-1.577538
H	1.446804	-4.915649	0.062370
H	0.047063	-4.307211	-0.825719
C	-5.845367	-0.119547	-1.203623
H	-6.366017	-1.020831	-0.878163
H	-6.480592	0.740999	-0.988419
H	-5.705373	-0.188392	-2.282000
C	-4.353221	3.303970	0.590354
H	-4.047088	3.911411	1.443105
H	-5.292916	2.810615	0.844230
H	-4.527665	3.976013	-0.249900
C	4.723836	1.068496	-0.164393
H	2.892633	1.683250	-1.092029
H	2.838246	1.647140	0.673712
C	5.447570	0.763644	-1.318701
C	6.834822	0.714663	-1.291249
C	7.518367	0.976016	-0.106866
C	6.807021	1.280592	1.047419
C	5.416654	1.324343	1.016842
H	4.919614	0.565291	-2.242979
H	7.384075	0.481450	-2.193339
H	8.599434	0.946046	-0.086715
H	7.332099	1.488710	1.969646
H	4.867268	1.567204	1.917678

_O_-benzyl-abyssomicin C
COSMO

Total energy = -9822.87 kcal/mol

O	-0.521357	-1.703968	-1.230721
O	-1.258569	-1.251740	2.188946
O	-3.491052	-1.094520	2.404371
O	2.690812	-0.224279	-0.270949
C	3.200108	1.129703	-0.233801
O	-3.660030	-1.798034	-1.783168
O	-1.839911	4.033672	-0.653974
C	0.951261	-1.676807	-1.022724
H	1.364594	-1.814407	-2.014965
C	1.357470	-2.791684	-0.056633
H	2.434175	-2.683668	0.071095
C	0.654693	-2.532041	1.307225
H	1.367925	-2.291612	2.094738
H	0.083992	-3.405360	1.621224
C	-0.311442	-1.361946	1.123926
C	-1.159774	-1.558147	-0.088011
C	-2.475824	-1.386780	0.208622
C	-2.538895	-1.225624	1.663902
C	1.284904	-0.278421	-0.470291
H	1.003114	0.445571	-1.233198
C	0.470390	-0.024822	0.837718
H	1.164150	0.116736	1.668674
C	-3.578639	-1.146645	-0.747975
C	-4.492640	0.045109	-0.468144
H	-4.649822	0.096123	0.608643
C	-3.730145	1.340031	-0.924972
H	-2.878721	1.055522	-1.548753
H	-4.390413	1.913556	-1.579040
C	-3.255310	2.284612	0.224980
H	-3.050288	1.668215	1.100963
C	-1.925156	2.897240	-0.201050
C	-0.740644	1.992740	-0.182094
H	-0.092386	2.089773	-1.045050
C	-0.521613	1.106893	0.790018
H	-1.174903	1.135150	1.653295
C	1.064057	-4.183579	-0.618104
H	1.572913	-4.334154	-1.571216
H	1.413664	-4.946077	0.078956
H	-0.006248	-4.335264	-0.771095
C	-5.846726	-0.105199	-1.161544
H	-6.350560	-1.018061	-0.840994
H	-6.483688	0.743753	-0.911407
H	-5.734227	-0.140095	-2.245046
C	-4.305278	3.328356	0.595890
H	-3.965960	3.947234	1.427667
H	-5.233070	2.838397	0.894837
H	-4.521719	3.981605	-0.249931
C	4.700325	1.089954	-0.177191
H	2.866830	1.653251	-1.132514
H	2.799595	1.651485	0.637511
C	5.441173	0.849966	-1.338198
C	6.830798	0.812230	-1.295344
C	7.497973	1.020934	-0.089415
C	6.768658	1.262997	1.071365
C	5.376710	1.295104	1.026137
H	4.926843	0.698463	-2.278631
H	7.392929	0.629643	-2.200903
H	8.578844	0.999446	-0.056987
H	7.280581	1.430554	2.009017
H	4.813326	1.489334	1.929709

***atrop*-*O*-benzyl-abyssomicin C**
VACUUM

Total energy = -9825.21 kcal/mol

O	-0.590309	-1.534435	-1.363181
O	-1.230213	-1.519101	2.121928
O	-3.464432	-1.275168	2.392571
O	2.646771	-0.203827	-0.338601
C	3.164323	1.111177	-0.076044
O	-3.884964	-1.568172	-1.747463
O	-2.242601	3.162875	1.655173
C	0.869298	-1.541662	-1.183989
H	1.270514	-1.546103	-2.193369
C	1.307900	-2.776641	-0.388138
H	2.383958	-2.662646	-0.250802
C	0.608270	-2.730531	1.003571
H	1.329478	-2.653051	1.817850
H	0.011625	-3.628029	1.169011
C	-0.327969	-1.520829	1.025467
C	-1.207660	-1.537091	-0.181873
C	-2.499610	-1.379200	0.162708
C	-2.535023	-1.370327	1.639236
C	1.235044	-0.236704	-0.457077
H	0.903672	0.599948	-1.077049
C	0.507616	-0.188456	0.925128
H	1.269183	-0.243671	1.704378
C	-3.631601	-0.976778	-0.716203
C	-4.337564	0.326097	-0.318769
H	-4.108301	0.526160	0.728116
C	-3.745327	1.474550	-1.200031
H	-4.500204	1.756046	-1.938550
H	-2.902827	1.106781	-1.790079
C	-3.328780	2.748972	-0.442375
H	-4.181405	3.126924	0.125780
C	-2.214848	2.562109	0.596368
C	-1.114147	1.620185	0.242212
H	-1.032477	1.342897	-0.801642
C	-0.385223	0.997580	1.170919
H	-0.549879	1.270930	2.207099
C	1.034706	-4.076634	-1.146065
H	-0.031263	-4.207439	-1.340472
H	1.379026	-4.933309	-0.564477
H	1.559030	-4.090447	-2.103534
C	-5.856731	0.208623	-0.470488
H	-6.261005	-0.535493	0.216926
H	-6.332431	1.166652	-0.250763
H	-6.116901	-0.086173	-1.487565
C	-2.880320	3.850122	-1.423996
H	-2.001939	3.540957	-1.996323
H	-2.632777	4.768224	-0.890213
H	-3.679745	4.070525	-2.133669
C	4.665381	1.066100	-0.075853
H	2.800162	1.795598	-0.850643
H	2.797086	1.478387	0.886304
C	5.362694	0.835742	-1.263388
C	6.750579	0.803572	-1.272989
C	7.461729	1.007680	-0.093130
C	6.776756	1.238425	1.093343
C	5.385363	1.264100	1.100063
H	4.813021	0.679672	-2.182991
H	7.279232	0.626575	-2.199905
H	8.543224	0.989472	-0.101475
H	7.322376	1.399599	2.013107
H	4.856625	1.445428	2.027318

***atrop*-*O*-benzyl-abyssomicin C**
COSMO

Total energy = -9801.63 kcal/mol

O	-0.579632	-1.623343	-1.323163
O	-1.322949	-1.544902	2.130544
O	-3.540165	-1.224376	2.346735
O	2.637650	-0.241171	-0.275292
C	3.110688	1.113828	-0.093622
O	-3.804695	-1.505045	-1.833770
O	-2.245383	3.082768	1.758357
C	0.891496	-1.639388	-1.110744
H	1.308199	-1.660501	-2.111184
C	1.287837	-2.864413	-0.283334
H	2.355855	-2.748876	-0.096279
C	0.528647	-2.811919	1.076980
H	1.213288	-2.755366	1.922010
H	-0.096604	-3.695660	1.203231
C	-0.370882	-1.578077	1.061999
C	-1.216347	-1.579939	-0.167033
C	-2.519510	-1.369319	0.142168
C	-2.587495	-1.353420	1.606642
C	1.226143	-0.317870	-0.399830
H	0.879776	0.495177	-1.038292
C	0.498786	-0.266565	0.982755
H	1.251601	-0.349153	1.766071
C	-3.595888	-0.928603	-0.772995
C	-4.302408	0.372305	-0.399748
H	-4.131316	0.549839	0.661572
C	-3.630141	1.525722	-1.220531
H	-4.338238	1.848571	-1.986081
H	-2.764805	1.153816	-1.771751
C	-3.225067	2.770819	-0.408932
H	-4.099580	3.156956	0.117900
C	-2.166479	2.528704	0.664987
C	-1.063421	1.600949	0.318533
H	-0.948212	1.371116	-0.732229
C	-0.371795	0.931293	1.245007
H	-0.545757	1.165017	2.288515
C	1.059837	-4.173909	-1.038419
H	0.002823	-4.321226	-1.268465
H	1.391876	-5.017650	-0.432268
H	1.621003	-4.185482	-1.973914
C	-5.812825	0.298164	-0.641845
H	-6.273674	-0.472930	-0.022557
H	-6.273260	1.255704	-0.393702
H	-6.026984	0.075650	-1.687623
C	-2.697033	3.877772	-1.346450
H	-1.801075	3.552272	-1.879071
H	-2.454774	4.781028	-0.785613
H	-3.459742	4.125891	-2.085563
C	4.611873	1.119890	-0.133747
H	2.701511	1.736382	-0.893200
H	2.754844	1.505672	0.861229
C	5.285345	0.941237	-1.345985
C	6.675117	0.949207	-1.390704
C	7.410319	1.142813	-0.221934
C	6.748367	1.324914	0.988450
C	5.355874	1.309757	1.031143
H	4.718301	0.800950	-2.257606
H	7.184469	0.813045	-2.334887
H	8.491226	1.155896	-0.257297
H	7.312756	1.479061	1.897861
H	4.844769	1.453968	1.974198

***O*-benzyl-desmethylabyssomicin C**
VACUUM

Total energy = -8525.12 kcal/mol

O	0.928294	1.246438	-1.446818
O	1.463199	1.268432	2.042720
O	3.681851	1.143792	2.409038
O	-2.350999	0.072945	-0.342169
C	-2.983128	-1.196951	-0.101680
O	3.842511	0.780412	-1.949548
O	2.631107	-3.761566	-1.088356
C	-0.539484	1.258622	-1.317966
H	-0.901535	1.264240	-2.340821
C	-0.965907	2.496722	-0.535220
H	-2.052161	2.555350	-0.542374
C	-0.416734	2.383538	0.907994
H	-1.210858	2.174101	1.624711
H	0.087371	3.297156	1.219294
C	0.598339	1.237598	0.919765
C	1.511246	1.288328	-0.260103
C	2.803284	1.136599	0.125620
C	2.790262	1.179157	1.603647
C	-0.955637	-0.029848	-0.580843
H	-0.763928	-0.882746	-1.232236
C	-0.122490	-0.156264	0.730121
H	-0.805401	-0.275677	1.573589
C	3.892242	0.629363	-0.740349
C	5.007615	-0.187266	-0.098021
H	5.094951	0.046668	0.960751
C	4.870131	-1.714725	-0.303028
H	4.721864	-1.929668	-1.363008
H	5.835076	-2.149804	-0.038483
C	3.780850	-2.452936	0.538166
H	3.510248	-1.857497	1.409713
C	2.568132	-2.829211	-0.303788
C	1.340664	-1.985703	-0.277211
H	0.813971	-2.004994	-1.223791
C	0.934074	-1.233087	0.745495
H	1.483387	-1.285173	1.679042
H	-0.570376	3.378003	-1.040192
H	5.927943	0.127590	-0.593455
H	4.199617	-3.393796	0.896079
C	-4.464276	-0.995080	0.031907
H	-2.761317	-1.868280	-0.937726
H	-2.578703	-1.653629	0.806353
C	-5.258314	-0.845048	-1.105804
C	-6.629079	-0.652772	-0.990688
C	-7.222905	-0.610444	0.267295
C	-6.440861	-0.760304	1.406663
C	-5.067898	-0.948802	1.287048
H	-4.799635	-0.882759	-2.085865
H	-7.234749	-0.542792	-1.879919
H	-8.291299	-0.467719	0.357455
H	-6.898093	-0.733669	2.386358
H	-4.462529	-1.069198	2.176728

***O*-benzyl-desmethylabyssomicin C**
COSMO

Total energy = -8550.18 kcal/mol

O	0.946062	1.279364	-1.421667
O	1.489281	1.272642	2.058808
O	3.696260	1.182361	2.433452
O	-2.349695	0.108788	-0.325540
C	-2.953580	-1.175616	-0.044443
O	3.837801	0.750735	-1.927953
O	2.577056	-3.725226	-1.204411
C	-0.539829	1.308056	-1.299121
H	-0.890474	1.326370	-2.323049
C	-0.934359	2.544579	-0.504466
H	-2.017627	2.634322	-0.516937
C	-0.397793	2.406206	0.940047
H	-1.193983	2.185462	1.649465
H	0.109037	3.312721	1.263593
C	0.608401	1.254463	0.936211
C	1.519783	1.305490	-0.240581
C	2.818507	1.138366	0.148083
C	2.798393	1.192381	1.618459
C	-0.953290	0.012825	-0.574474
H	-0.771325	-0.828528	-1.239492
C	-0.114703	-0.135718	0.731993
H	-0.783924	-0.270889	1.582357
C	3.887446	0.605130	-0.706171
C	4.979820	-0.236298	-0.073112
H	5.050025	-0.034403	0.991983
C	4.836408	-1.758827	-0.311698
H	4.720654	-1.955885	-1.379357
H	5.790631	-2.198678	-0.023091
C	3.723619	-2.505608	0.488316
H	3.452868	-1.942219	1.379037
C	2.513671	-2.821855	-0.368776
C	1.297802	-1.982336	-0.314559
H	0.730509	-2.006010	-1.236842
C	0.938661	-1.214445	0.717604
H	1.511479	-1.277864	1.634916
H	-0.517751	3.420921	-0.998966
H	5.915635	0.080660	-0.536692
H	4.124304	-3.464653	0.816125
C	-4.442181	-1.006098	0.051771
H	-2.698853	-1.869261	-0.848092
H	-2.553726	-1.572747	0.890941
C	-5.238871	-1.115605	-1.090661
C	-6.618584	-0.953684	-1.009275
C	-7.217545	-0.681156	0.218484
C	-6.431484	-0.570128	1.363008
C	-5.051538	-0.733425	1.278218
H	-4.777439	-1.335905	-2.044836
H	-7.225088	-1.047096	-1.899689
H	-8.290410	-0.560950	0.283445
H	-6.892010	-0.364494	2.319531
H	-4.445076	-0.656368	2.171691

***atrop*-*O*-benzyl-desmethylabyssomicin C (1)**
VACUUM

Total energy = -8526.49 kcal/mol

O	0.926017	1.524741	-1.256875
O	1.738597	0.986932	2.149983
O	3.968414	0.601114	2.251386
O	-2.325623	0.231065	-0.246178
C	-2.920210	-1.074421	-0.138141
O	4.121666	1.363180	-1.883695
O	2.350441	-3.707686	0.977155
C	-0.520090	1.572096	-0.999687
H	-0.970191	1.739070	-1.973296
C	-0.833038	2.694693	-0.014383
H	-1.912352	2.725816	0.127041
C	-0.093211	2.425745	1.323471
H	-0.787479	2.250027	2.145627
H	0.547837	3.262359	1.598468
C	0.783446	1.186516	1.118539
C	1.599519	1.332935	-0.124380
C	2.896263	1.059608	0.118551
C	3.006822	0.842807	1.575597
C	-0.922836	0.198328	-0.439386
H	-0.673092	-0.562121	-1.183849
C	-0.127141	-0.078008	0.879929
H	-0.845453	-0.096342	1.700653
C	3.935276	0.700352	-0.881001
C	4.623058	-0.645078	-0.672076
H	4.537546	-0.962737	0.366275
C	4.007860	-1.703244	-1.641835
H	4.758844	-1.973726	-2.384728
H	3.199631	-1.247449	-2.216518
C	3.517427	-3.002327	-0.983809
H	4.337897	-3.533528	-0.499844
C	2.396227	-2.917053	0.052359
C	1.380484	-1.839376	-0.123960
H	1.313743	-1.390763	-1.108573
C	0.703129	-1.332516	0.909014
H	0.858230	-1.786531	1.881282
H	-0.522024	3.643594	-0.451118
H	5.682976	-0.512762	-0.890729
H	3.142932	-3.668818	-1.771271
C	-4.415842	-0.941713	-0.132353
H	-2.594163	-1.683741	-0.987943
H	-2.578256	-1.571010	0.774339
C	-5.100404	-0.661183	-1.316283
C	-6.483767	-0.542580	-1.322844
C	-7.203173	-0.710219	-0.142648
C	-6.531048	-0.989296	1.041191
C	-5.144280	-1.102899	1.044294
H	-4.544699	-0.536178	-2.237131
H	-7.002307	-0.328946	-2.247711
H	-8.281553	-0.626103	-0.148101
H	-7.084348	-1.123440	1.960689
H	-4.625934	-1.325381	1.968464

***atrop*-*O*-benzyl-desmethylabyssomicin C (1)**
COSMO

Total energy = -8551.92 kcal/mol

O	0.934343	1.567765	-1.227993
O	1.794292	0.995228	2.152050
O	4.007003	0.587222	2.232335
O	-2.319920	0.256178	-0.214750
C	-2.887070	-1.073279	-0.153441
O	4.076910	1.340913	-1.922958
O	2.324735	-3.695207	1.027628
C	-0.523319	1.630639	-0.957841
H	-0.973202	1.809131	-1.926667
C	-0.798625	2.749147	0.039126
H	-1.873698	2.798403	0.201193
C	-0.041956	2.467787	1.364689
H	-0.724625	2.294502	2.195427
H	0.613719	3.296041	1.626515
C	0.807816	1.216293	1.137710
C	1.607404	1.354223	-0.113164
C	2.910678	1.052330	0.110700
C	3.031491	0.837117	1.555011
C	-0.914161	0.248299	-0.409881
H	-0.659776	-0.497618	-1.163831
C	-0.123834	-0.033829	0.912274
H	-0.835277	-0.035552	1.737464
C	3.910585	0.671324	-0.908232
C	4.581827	-0.676099	-0.731798
H	4.534063	-0.991801	0.308882
C	3.894963	-1.724765	-1.668019
H	4.604006	-2.008698	-2.444304
H	3.060260	-1.263844	-2.197101
C	3.424882	-3.015152	-0.981030
H	4.263577	-3.548745	-0.533065
C	2.339897	-2.914094	0.078607
C	1.324485	-1.846998	-0.086681
H	1.224561	-1.435409	-1.082912
C	0.687783	-1.299525	0.952789
H	0.855675	-1.718194	1.937854
H	-0.483752	3.694608	-0.398143
H	5.632673	-0.572681	-1.000783
H	3.009805	-3.677217	-1.750551
C	-4.385335	-0.968439	-0.162020
H	-2.538799	-1.642559	-1.018296
H	-2.545093	-1.579588	0.751435
C	-5.064871	-0.698598	-1.353580
C	-6.451803	-0.600743	-1.370741
C	-7.178612	-0.779548	-0.194546
C	-6.510852	-1.050488	0.995935
C	-5.120828	-1.142950	1.010739
H	-4.504346	-0.569992	-2.270770
H	-6.966063	-0.394857	-2.299554
H	-8.257902	-0.711049	-0.208369
H	-7.069342	-1.193096	1.910864
H	-4.605440	-1.358165	1.937837

5 References

[1] For description of the technique of dry-flash chromatography, see: a) L. M. Harwood, *Aldrichimica Acta* **1985**, *18*, 25; b) *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific&Technical, 5th edition, London, 1989, p. 220; c) A recent account which includes some improvements of the separation technique: D. S. Pedersen, C. Rosenbohm, *Synthesis* **2001**, 2431-2434.

[2] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, **1988**.

[3] J. A. Ibers, W. C. Hamilton, *International Tables for X-ray Crystallography*, Kynoch Press, Birmingham,**1974**.

[4] SIR-92: A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, *J. Appl. Cryst.***1993**, *26*, 343.

[5] Mercury: visualization and analysis of crystal structures, C. F. Macrae, P. R. Edgington, P. McCabe,E. Pidcock, G. P. Shields, R. Taylor, M. Towler, J. Van de Streek, *J. Appl. Cryst.* **2006**, *39*, 453.

[6] M. Sheldrick, SHELXL-97, Program for crystal structure refinement, University of Goettingen, Germany, **1997**.

[7] a) J. A. Macritchie, A. Silcock, C. L. Willis, *Tetrahedron Asymmetry*, **1997**, *8*, 3895; b) J. T. Moore, N. V. Hanhan, M. E. Mahoney, S. P. Cramer, J. T. Shaw, *Org. Lett.*, **2013**, *15*, 5615.

[8] a) M. N. Paddon-Row, A. I. Longshaw, A. C. Willis, M. S. Sherburn, *Chemistry – An Asian Journal*, **2009**, *4*, 126; b) K. Mori, *Tetrahedron,* **1974**, *30*, 3807.

[9] M. P. Schneider, M. Goldbach, *J. Am. Chem. Soc*. **1980,** *102*, 1461.

[10] a) M. J. Wanner, S. Ingemann, J. H. van Maarseveen, H. Hiemstra, *Eur. J. Org. Chem*, **2013**, *6*, 1100; b) A. Nakamura, S. Lectard, D. Hashizume, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc*, **2010**, *132*, 4036.

[11] a) K. J. Frankowski, J. E. Golden, Y. Zeng, Y. Lei, J. Aube, *J. Am. Chem. Soc,* **2008**, *130*, 6018; b) Y. Lu, G. Zou, G. Zhao, *ACS Catal*. **2013***, 3*, 1356.

[12] J. Riedlinger, A. Riecke, H. Zahner, B. Krismar, A. T. Bull, L. A. Maldonado, A. C. Ward, M. Goodffellow, B. Bister, D. Bischoff, R. D. Sussmuth, H. -P. Fiedler, *J. Antibiot*. **2004**, *7*, 271.

[13] T. Mosmann, *J. Immunol. Meth*. **1983**, *65*, 55.

[14] T. Ohno, T. Abe, *J. Immunol. Meth*. **1991**, *145*, 199.

[15] ADF2013.01. SCM, Theoretical Chemistry, Vrije Universiteit Amsterdam, The Netherlands, http://www.scm.com, **2013**.

[16] C. F. Guerra, J. G. Snijders, G. te Velde, E. J. Baerends, *Theor. Chem. Acc*. **1998**, *99*, 391.

[17] G. te Velde, F. M. Bickelhaupt, S. J. A. van Gisbergen, C. F. Guerra, E. J. Baerends, J. G. Snijders, T. Ziegler, *J. Comput. Chem*. **2001**, *22*, 931.

[18] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.

[19] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.

[20] D. Reinen, M. Atanasov, P. Köhler, D. Babel *Coord. Chem. Rev*. **2010**, *254*, 2703.

[21] A. Bérces, R. M. Dickson, L. Fan, H. Jacobsen, D. Swerhone, T. Ziegler, *Comput. Phys. Commun*. **1997**, *100*, 247.

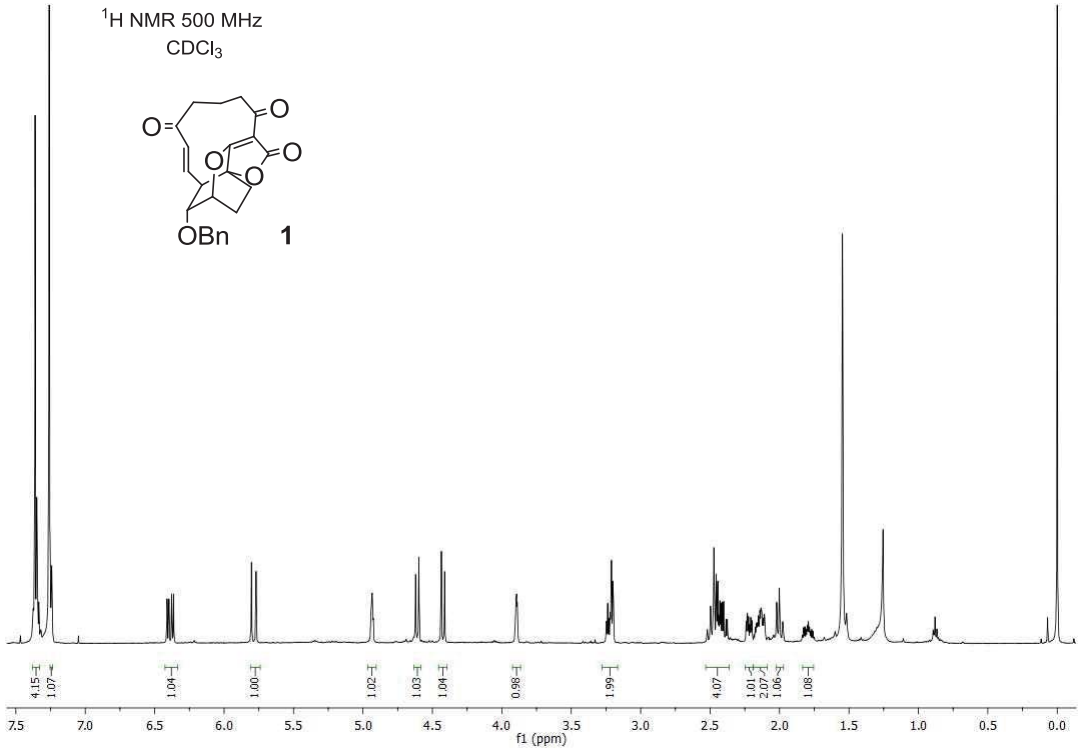
[22] H. Jacobsen, A. Bérces, D. Swerhone, T. Ziegler, *Comput. Phys. Commun*. **1997**, *100*, 263.

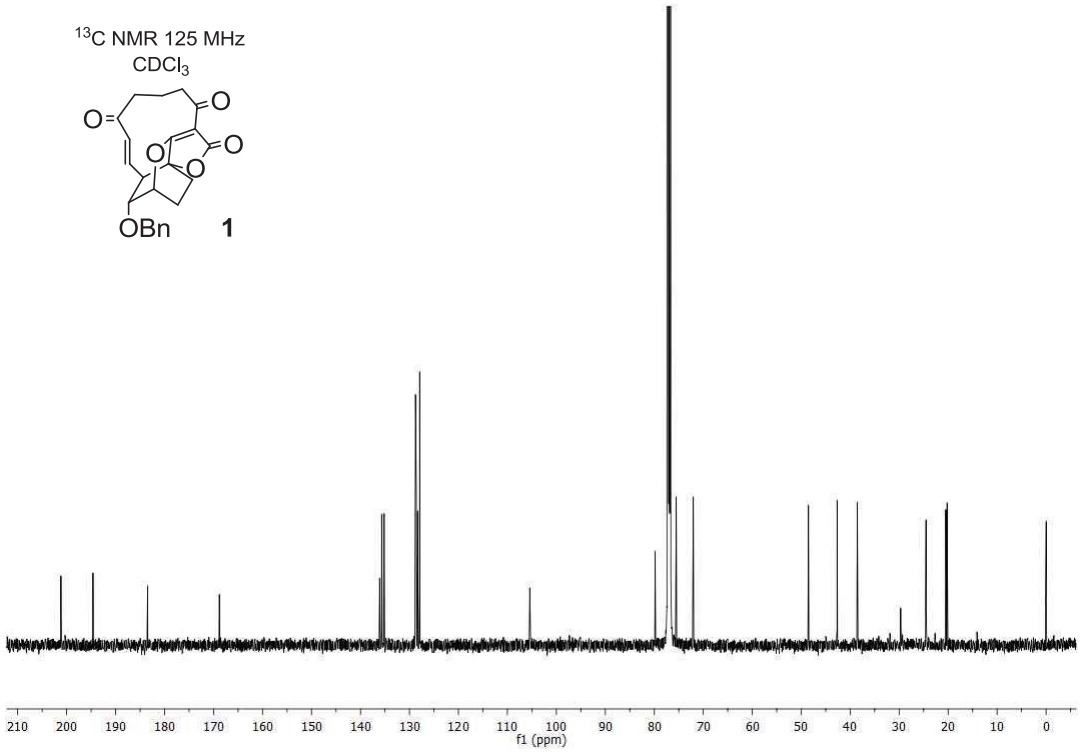
[23] F. L. Hirshfeld, *Theor.Chim.Acta* **1977**, *44*, 129.

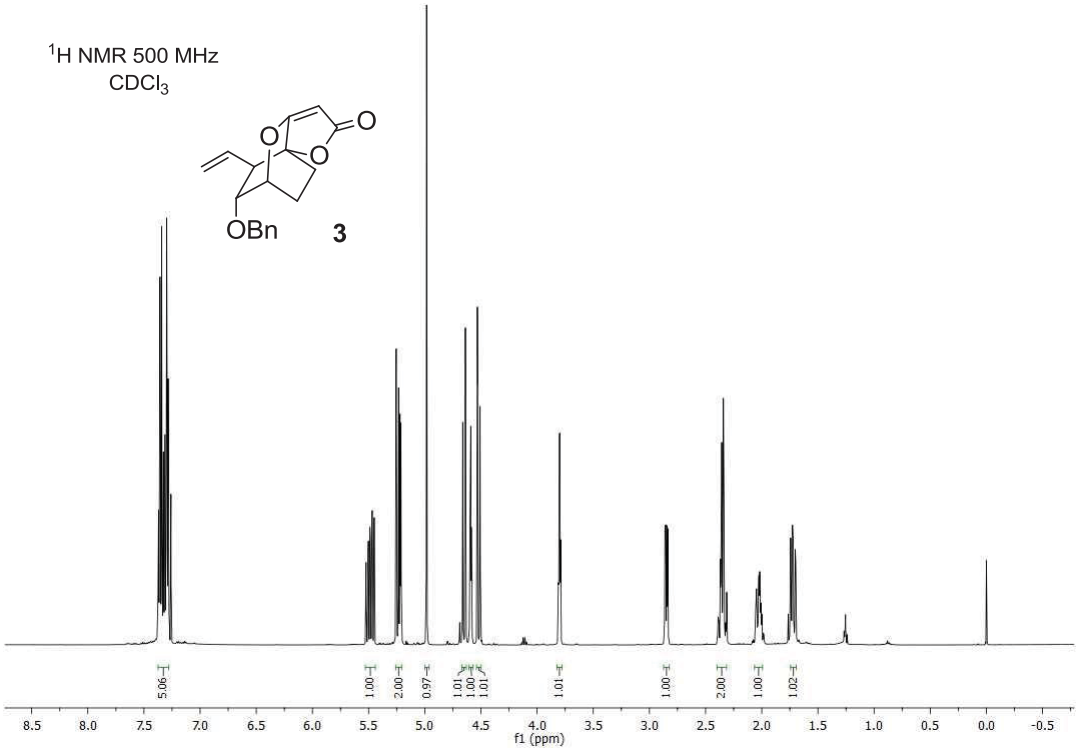
[24] G. te Velde, F. M. Bickelhaupt, E. J. Baerends, C. F. Guerra, S. J. A. van Gisbergen, J. G. Snijders, T. Ziegler *J. Comput. Chem.* **2001**, *22*, 931.

[25] M. Swart, P. Th. van Duijnen, J. G. Snijders, *J. Comput. Chem.* **2001**, *22*, 79.

6 Copies of spectra



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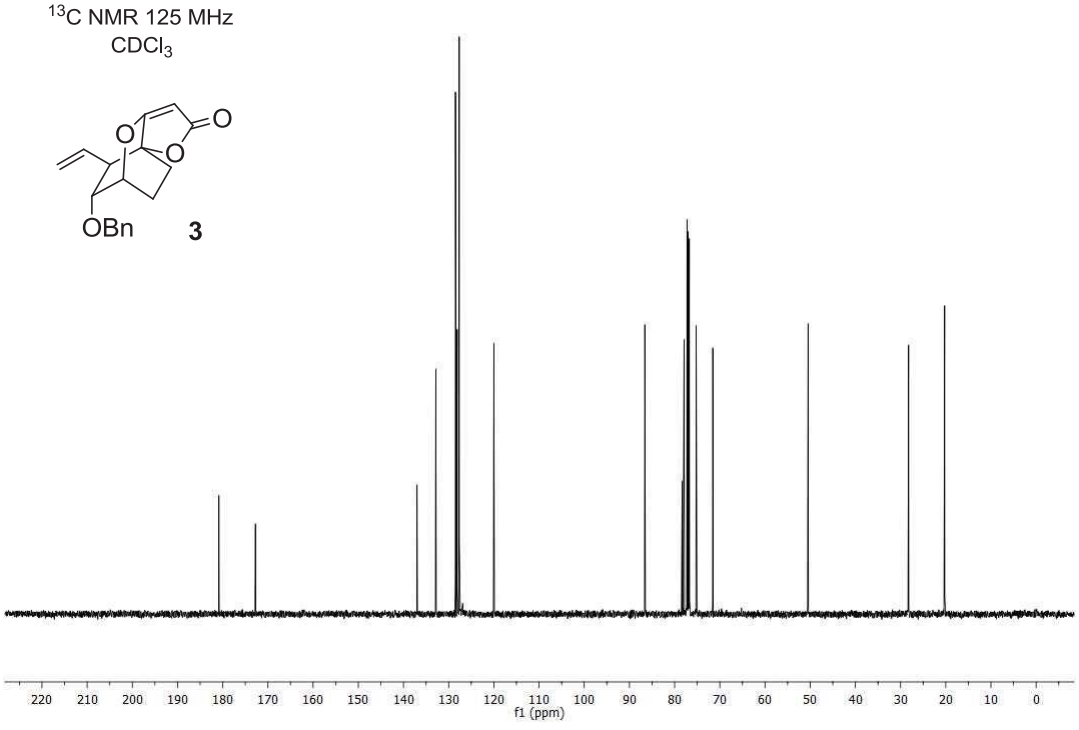
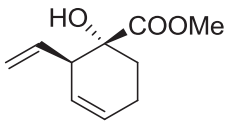
O
O
O
OBn
3
5.06
1.00
2.00
0.97
1.01
1.00
1.01
1.01
1.00
2.00
1.00
1.02
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

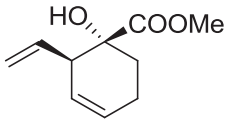

^{13}C NMR 125 MHz
$CDCl_3$
O
O
O
OBn
3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

^{1}H NMR 500 MHz
$CDCl_3$



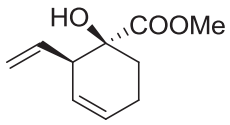
5a

^{13}C NMR 125 MHz
$CDCl_3$



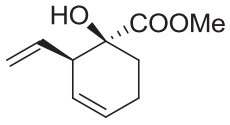
5a

^{1}H NMR 500 MHz
$CDCl_3$

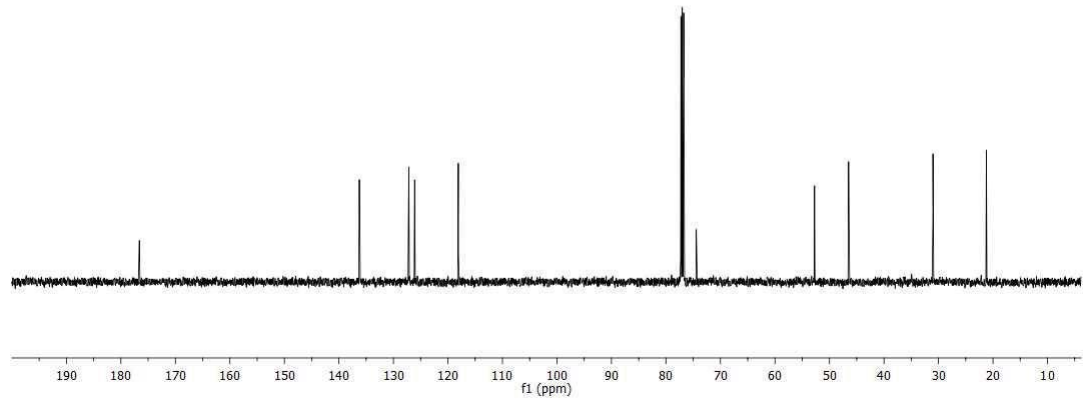


***epi*-5a**

^{13}C NMR 125 MHz
$CDCl_3$



***epi*-5a**



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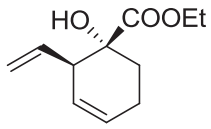
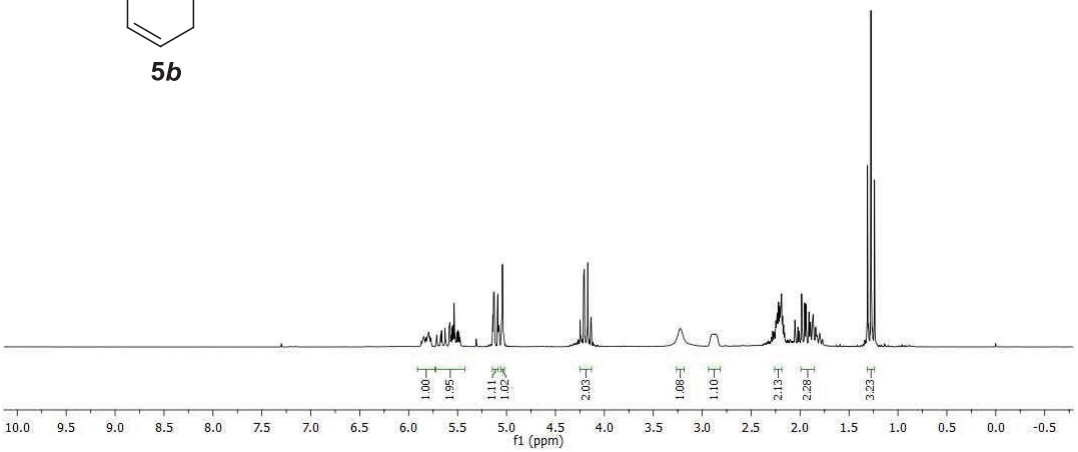
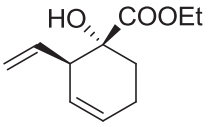
$CDCl_3$



5b



APT NMR 50 MHz
$CDCl_3$



5b

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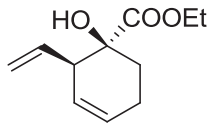

***epi*-5b**

APT NMR 50 MHz
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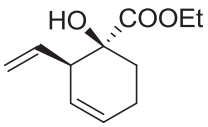

***epi*-5b**

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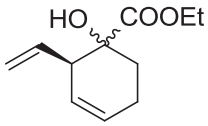
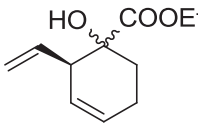


5c and *epi*-5c

^{13}C NMR 125 MHz
$CDCl_3$



5c and *epi*-5c

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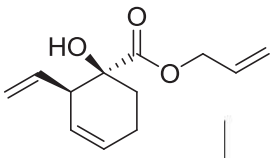
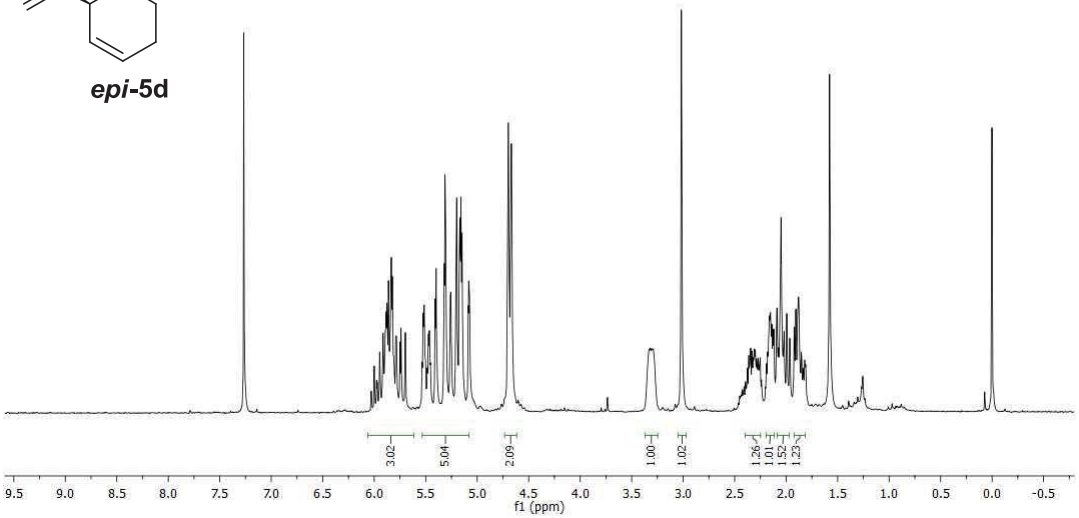


***epi*-5d**



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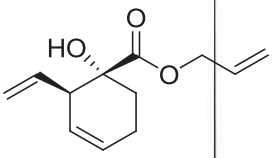
$CDCl_3$



5d

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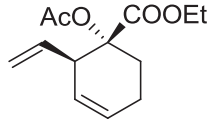
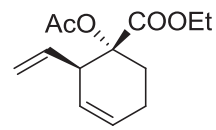


5e

APT NMR 50MHz
$CDCl_3$



5e

^{1}H NMR 200 MHz
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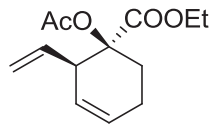
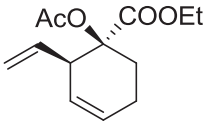


***epi*-5e**

APT NMR 50MHz
$CDCl_3$



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^{1}H NMR 200 MHz
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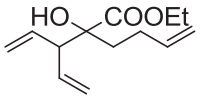

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APT NMR 50MHz
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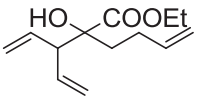

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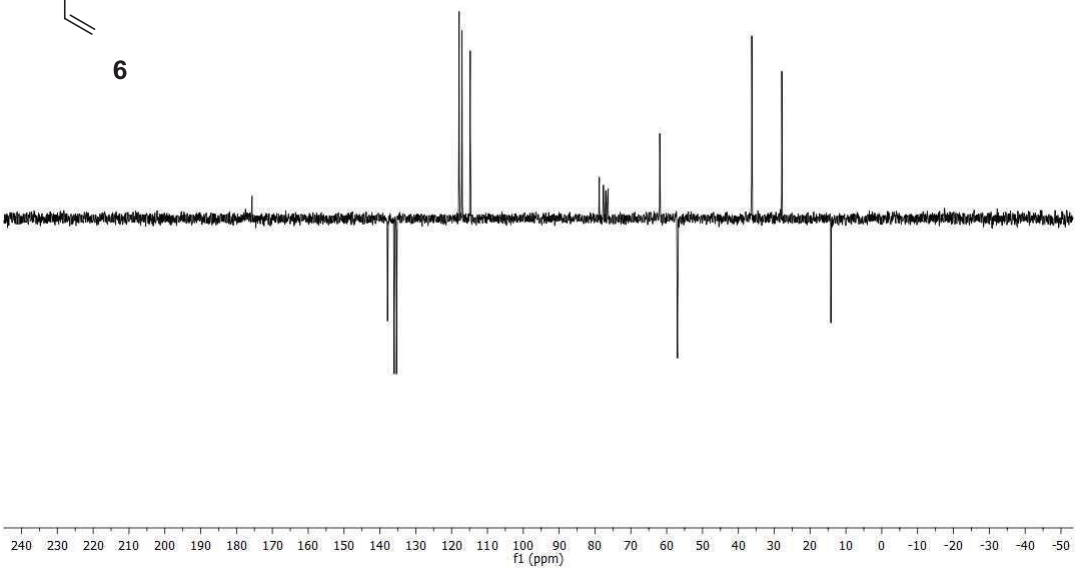
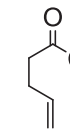


^{1}H NMR 200 MHz

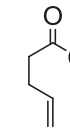
$CDCl_3$



7

^{13}C NMR 50 MHz

$CDCl_3$



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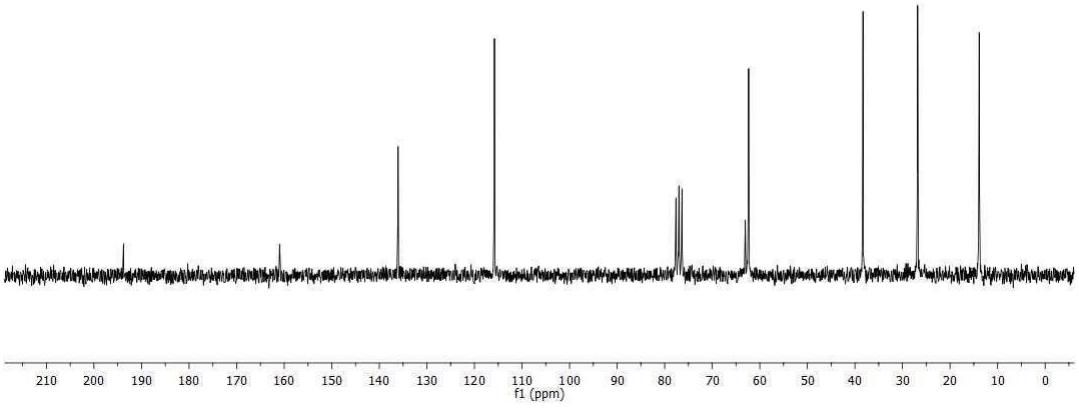

^{1}H NMR 200 MHz
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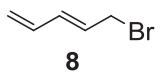

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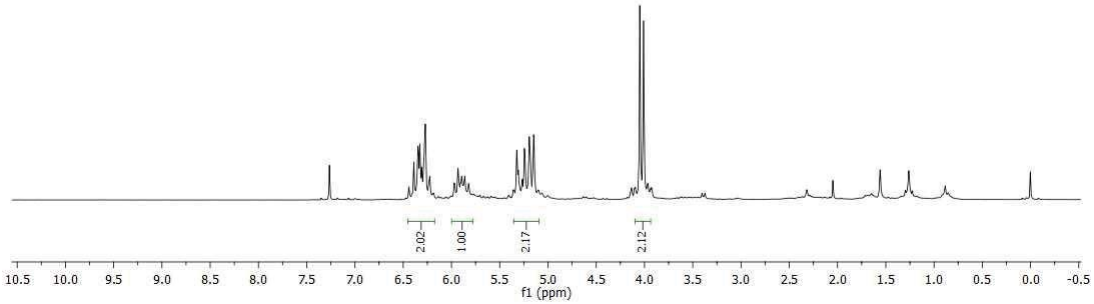

^{13}C NMR 50 MHz
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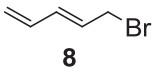

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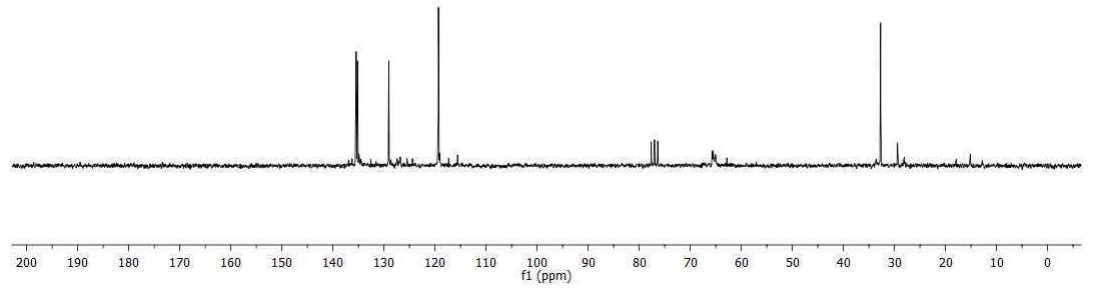

^{1}H NMR 200 MHz
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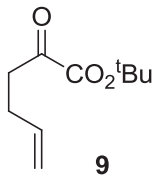
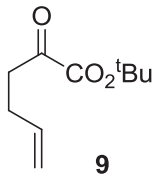


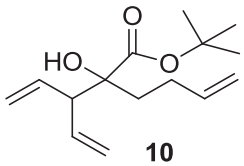
9

APT NMR 50 MHz
$CDCl_3$



9

^{1}H NMR 200 MHz
$CDCl_3$



10

APT NMR 50 MHz
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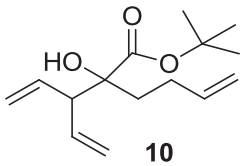
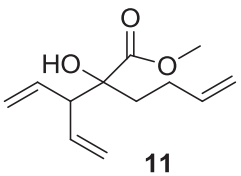


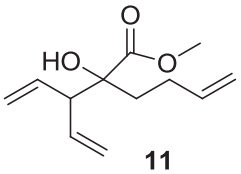
10

^{1}H NMR 200 MHz
$CDCl_3$



11

^{13}C NMR 50 MHz
$CDCl_3$



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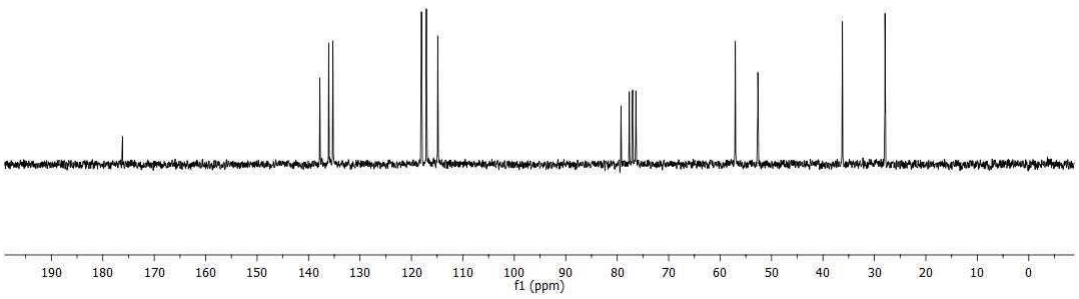

^{1}H NMR 200 MHz
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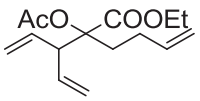
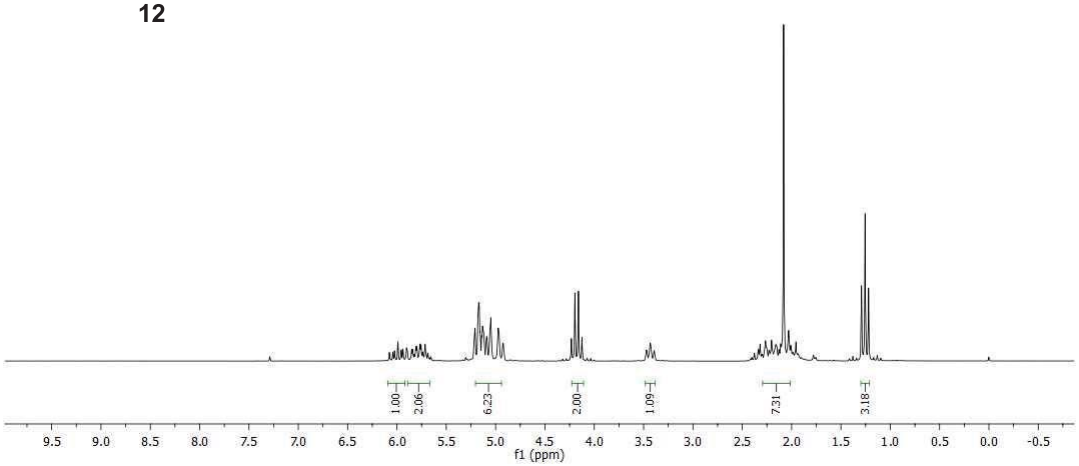
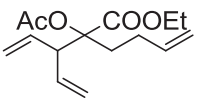


12



APT NMR 50MHz
$CDCl_3$



12

^{1}H NMR 200 MHz
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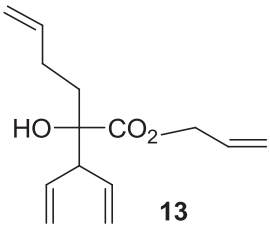
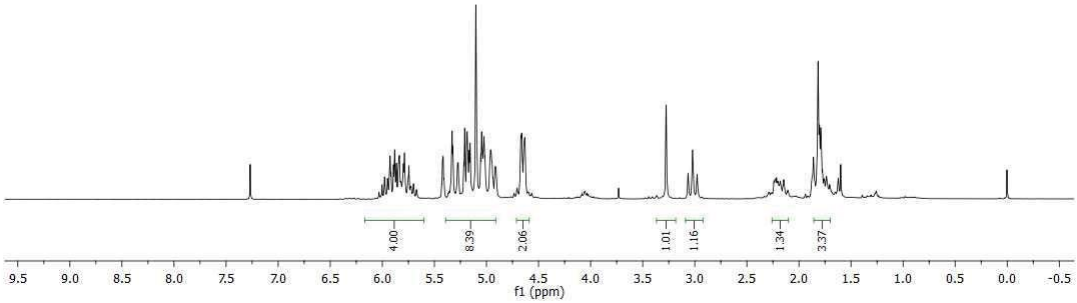
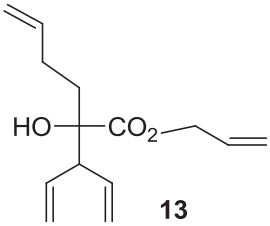


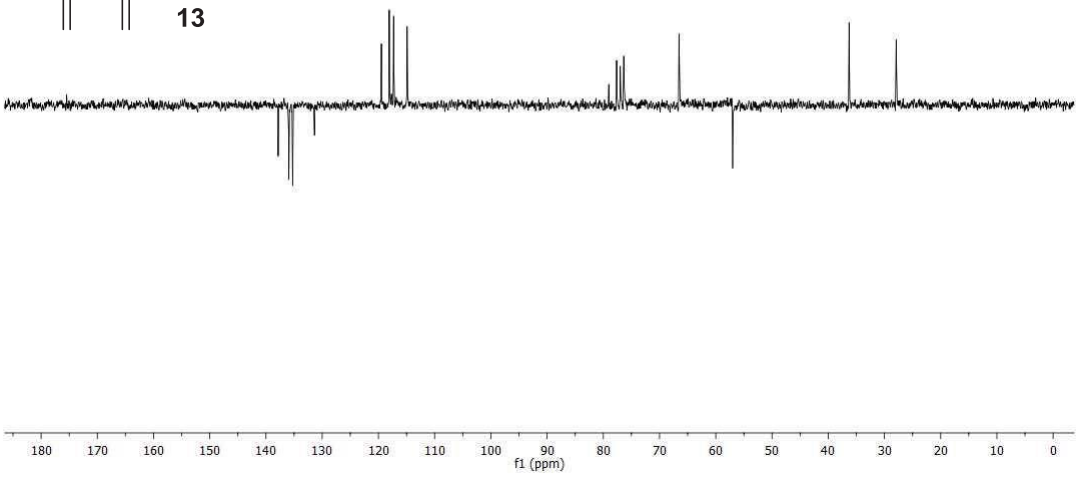
13



APT NMR 50 MHz
$CDCl_3$



13



^{1}H NMR 200 MHz
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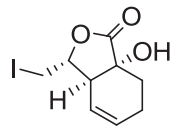
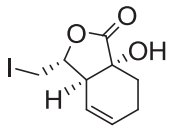


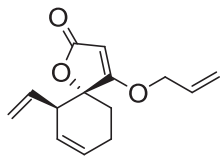
14

APT NMR 50MHz
$CDCl_3$



14

^{1}H NMR 200 MHz
$CDCl_3$



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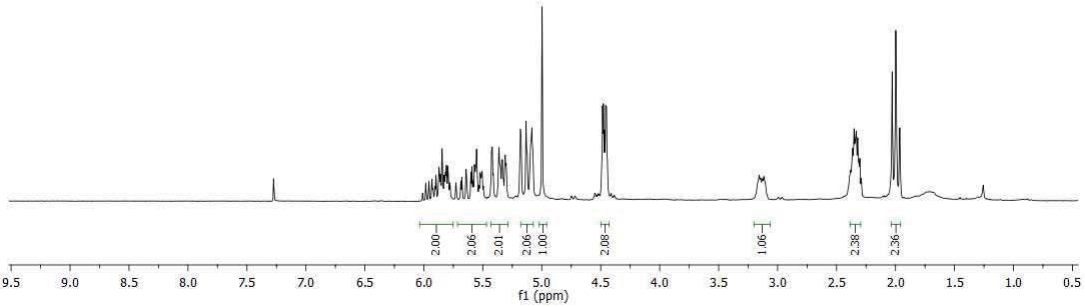
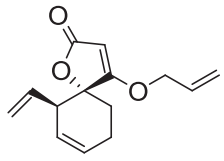
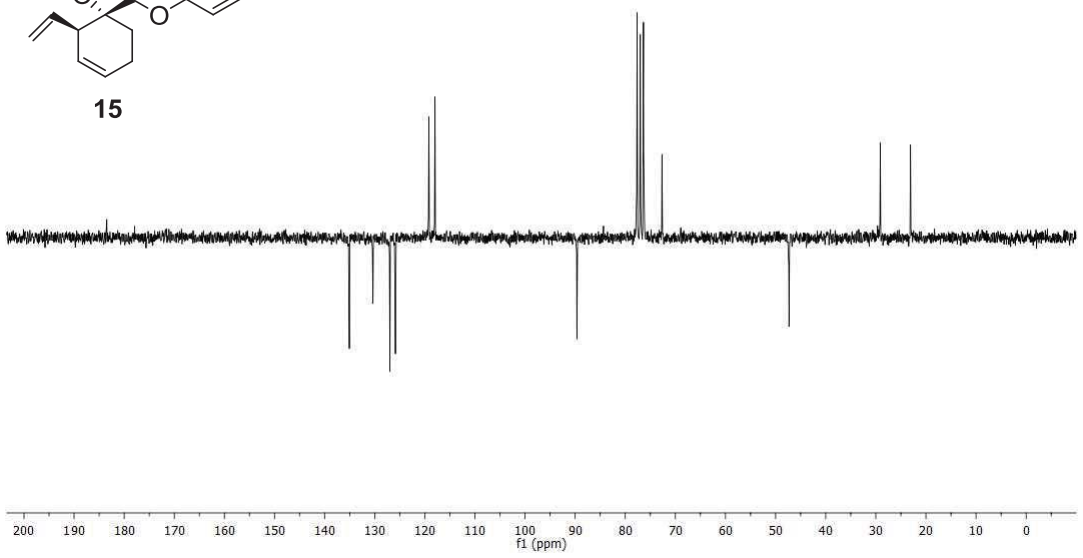


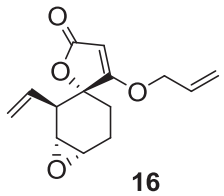
APT 50MHz
$CDCl_3$



15

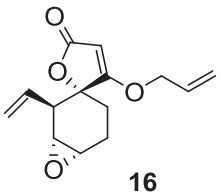


^{1}H NMR 500 MHz
$CDCl_3$



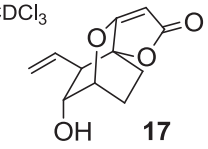
16

^{13}C NMR 125 MHz
$CDCl_3$

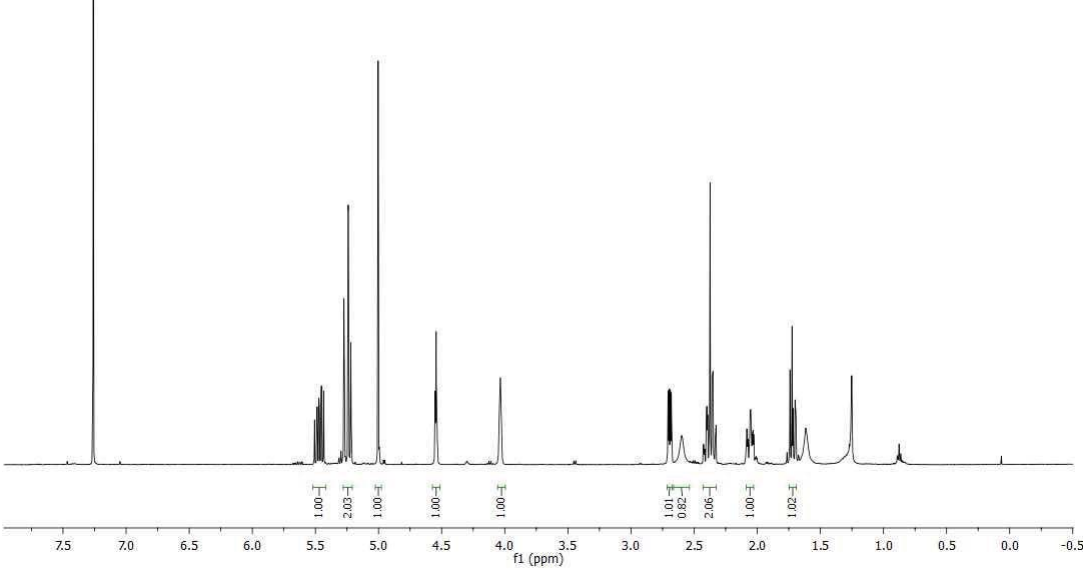


16

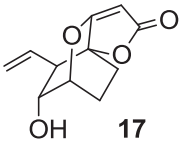
^{1}H NMR 500 MHz
$CDCl_3$



17

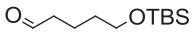


^{13}C NMR 125 MHz
$CDCl_3$

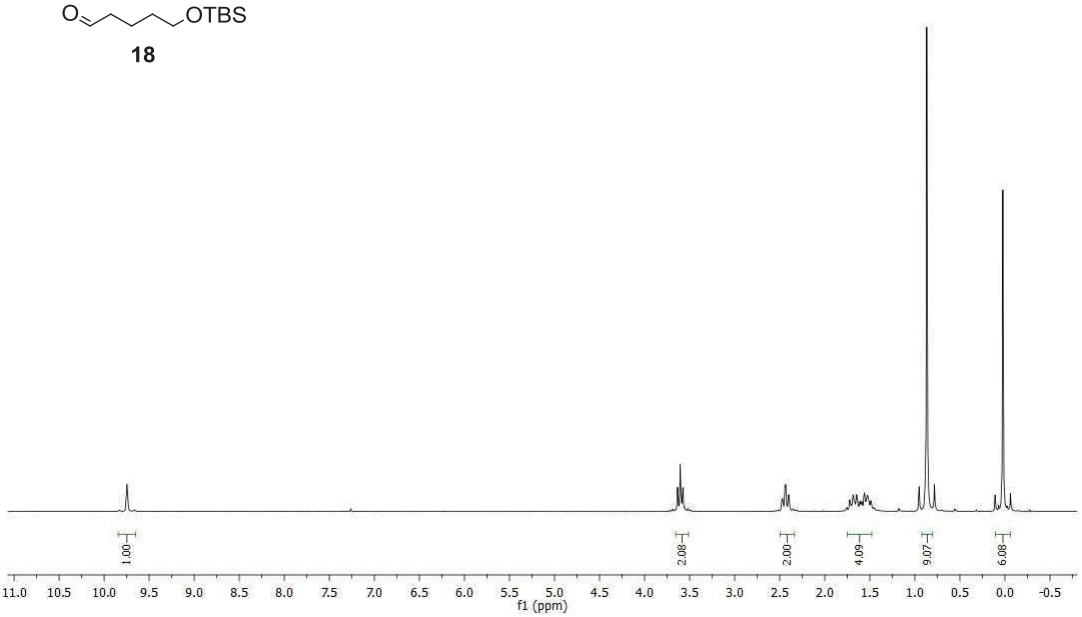


17

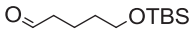
^{1}H NMR 500 MHz
$CDCl_3$



18

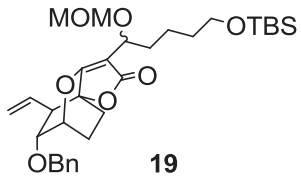


^{13}C NMR 125 MHz
$CDCl_3$



18

^{1}H NMR 500 MHz
$CDCl_3$



19

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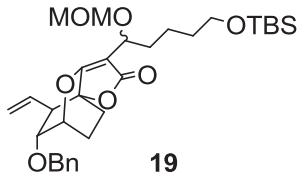
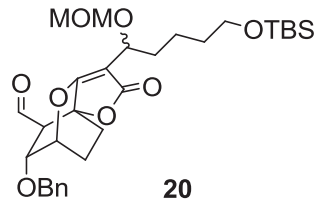


19

^{1}H NMR 500 MHz
$CDCl_3$



20

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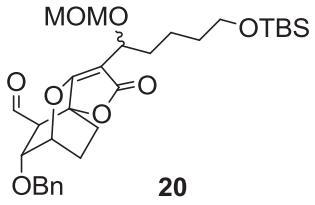

20

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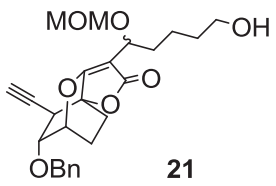

21

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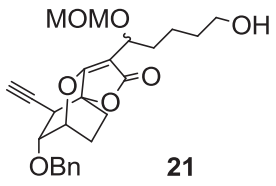

21

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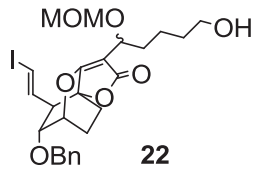
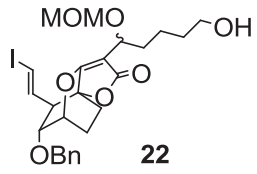
$CDCl_3$



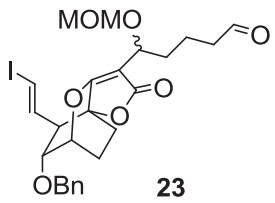
22

^{13}C NMR 125 MHz
$CDCl_3$



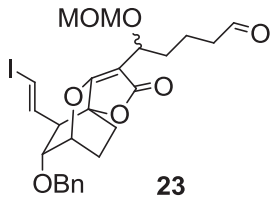
22

^{1}H NMR 500 MHz
$CDCl_3$



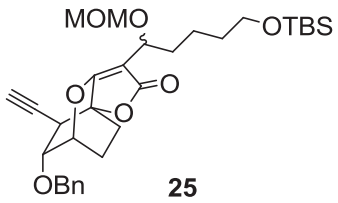
23

^{13}C NMR 125 MHz
$CDCl_3$



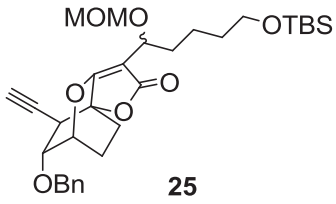
23

^{1}H NMR 500 MHz
$CDCl_3$



25

^{13}C NMR 125 MHz
$CDCl_3$



25

^{1}H NMR 200 MHz
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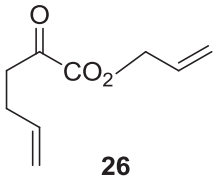
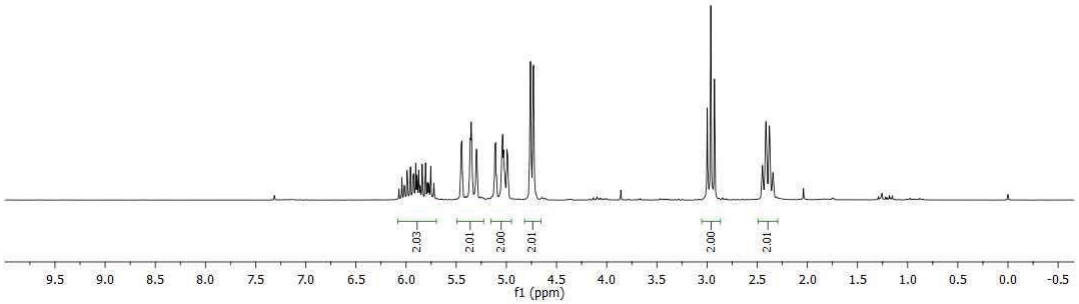
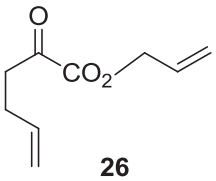


26



APT NMR 50 MHz
$CDCl_3$



26